How a structured exercise programme involving cardio and resistance exercise affects type 2 diabetes mellitus volunteers

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Abstract

Background T2DM is a metabolic disorder that is rapidly increasing in prevalence, it has become a 21st century epidemic and addressing this is one of the greatest global health challenges of our time. In the UK £10.3 billion or 10% of the NHS budget was spent on diabetes mellitus. It is essential that a prevention approach to T2DM is utilised within the NHS.

Aims The aims of this study are to compare physiological, metabolic parameters and inflammatory markers from type 2 diabetes mellitus (T2DM) and non-diabetic (ND) volunteers over a 6-week exercise period.

Methods This was a very interesting study where T2DM and ND volunteers completed one of three structured exercise programmes involving either a combination of cardio and resistance exercise, cardio exercise or resistance exercise twice a week for 6-weeks. Various parameters were recorded at baseline to compare with results after 1 exercise session and again after 12 exercise sessions.

Key findings Oral glucose tolerance test area under the curve results showed noticeable reductions from 1612.40 to 1354.10 mmol/L*min. Weight reduced by 2.58 kg in the T2 combination group after intervention which showed a statistically significant reduction from before to after intervention with a p-value of 0.049. Time to peak reduced in the T2 resistance group from 80 to 47 minutes. Total cholesterol reduced in the T2 resistance group after intervention from 5.34 to 4.68 mmol/L. Inflammatory marker results are also presented at the end of the results chapter.

Table of Contents

List of Figures

List of Tables

Chapter 1 Introduction

1.1 Aims of the study

The aims of this work are to compare the physiological and metabolic parameters from type 2 diabetes mellitus (T2DM) and non-diabetic volunteers over a 6-week exercise period. The reason for making the comparison is to compare T2DM volunteers with non-diabetic volunteers with respect to exercise and to compare the different components of exercise for effectiveness in each group. The parameters to be measured are anthropometric factors, blood pressure, heart rate, fasting blood glucose, oral glucose tolerance tests (OGTT), glycated haemoglobin (HbA1c), lipid profile and inflammatory markers for T2DM volunteers and healthy counterparts, undergoing resistance and cardiovascular exercise alone and in combination. It is well known that exercise is beneficial in overweight, pre-diabetic and diabetic individuals but less is understood about the detail (Zou et al., 2016). Previous work has shown changes in glucose homeostasis and inflammatory markers for type 1 diabetes mellitus (T1DM) and T2DM but comparisons against individual components of the exercise program remain to be discovered (Alblihed, 2013; Fève and Bastard, 2009; Kadoglou et al., 2007).

1.2 Background and history

T2DM is a metabolic disorder that is rapidly increasing in prevalence, it has become a 21st century epidemic and addressing this is one of the greatest global health challenges of our time (Jaacks et al., 2016). The first discovered historical evidence of diabetic symptoms is from 1552 B.C. when Hesy-Ra, Egyptian physician, documented frequent urination as a symptom of a mysterious disease that also caused emaciation. Then in 1912 the first modern mention of diabetes mellitus in an academic paper was by Hodgson (Hodgson, 1912). In 1916 Nicolae Paulescu discovered what he called “pancreine” a watery pancreatic extract which, when injected into a dog with diabetes, had a normalising effect on its blood glucose (BG) levels. It was an extract of bovine pancreas in salted water neutralised with hydrochloric acid and sodium hydroxide. During the time that Banting and Charles Best had isolated insulin in February 1922 and was successfully administered in a human patient for the first time, Paulescu was awaiting confirmation on his patent. When Banting and Macleod were awarded the Nobel prize in 1923 for insulin, Paulescu wrote to the Nobel committee claiming priority but his claims were rejected.

Normoglycaemia is the normal level of BG as opposed to hyperglycaemia which refers to high levels of BG and hypoglycaemia which means low levels of BG. T2DM occurs when insulin is produced by the pancreas in abnormally high and then low amounts attempting to maintain normoglycaemia, or the insulin has become ineffective to maintain normoglycaemia due to the body’s built up insulin resistance. The most common variations of Diabetes Mellitus are Type 1 Diabetes Mellitus (T1DM), T2DM, Gestational Diabetes Mellitus (GDM), Latent autoimmune diabetes of adulthood (LADA) and Maturity onset diabetes of young (MODY). 424.9 million adults worldwide and 58 million adults in Europe have diabetes in 2017 and by 2045 this will rise to 628.6 million worldwide and 66.7 million in Europe (International Diabetes Federation, 2017). T2DM is usually preventable through diet and exercise changes whereas T1DM is unexpected and autoimmune-based and is at present incurable and non-preventable.

In the UK £10.3 billion was spent on diabetes in 2015, 10% of the NHS budget (Cannell, 2016). A prevention approach to T2DM would be much more beneficial for the patient and society. Prevention would reduce the prevalence of T2DM and therefore the cost of treatment to the NHS. Prevention would include the promotion of regular exercise and a healthy diet. Globally It is estimated that 12% of global health expenditure is spent on diabetes.

The basis of recommending regular physical exercise for T2DM treatment or prevention is that exercise rapidly increases the rate of glucose uptake in contracting skeletal muscle (Richter, Derave and Wojtaszewski, 2001; Hayashi, Wojtaszewski and Goodyear, 1997; Holloszy and Hansen, 1996; Lund et al., 1995). Regular exercise training has beneficial effects on preventing the onset of T2DM and improving glycaemic control in those with pre-diabetes (Hordern et al., 2012). It is recommended that patients with T2DM pre-diabetes accumulate a minimum of 210 minutes per week of moderate intensity exercise or 125 minutes per week of vigorous intensity exercise with no more than two consecutive days without training as there is compelling evidence that T2DM is more likely to develop in individuals who have low physical activity and physical fitness (Hordern et al., 2012).

Obesity without the intervention of a healthy diet combined with regular exercise will cause prediabetes and eventually lead to T2DM. The modern lifestyle of sedentary office jobs combined with the ready meal diet has caused a huge rise in obesity. Unhealthy changes in eating habits and sedentary lifestyles are the main contributors to T2DM (Matzenbacher Dos Santos et al., 2015). An important part of preventing obesity and T2DM is the promotion of a healthy balanced diet. The root cause of this is the obesogenic environment of the UK, although there has been a trend of health and fitness recently that is still growing. It has become almost impossible to avoid sugary and processed foods throughout the western society, even in hospitals. The UK government have tried to change the obesogenic environment by bringing in taxes for unhealthy foods to positively influence the populations diet and prevent obesity. Thus, the new “sugar tax” was introduced in the UK in 2018 (Triggle, 2016). AG Barr, the company that produces Irn-Bru, announced in 2017 that due to the sugar tax it would cut the drinks sugar content down from about 10 g per 100 ml to just below 5 g (BBC, 2018).

1.3 Metabolic syndrome

Metabolic syndrome (MetS) is a collection of symptoms that links obesity with other unhealthy signs (Kaur, 2014). Two or more of the following symptoms are a sign of MetS (Wang, Q., Chair and Wong, 2017).

- increased blood pressure (Over 130/85 mmHg)
- hyperglycaemia
- excess fat around the waist
- high triglyceride levels
- low levels of high-density lipoproteins

Having any of these symptoms will increase the risk of developing DM and cardiovascular disease. However, when all these symptoms are present together there is a further much-increased risk of developing DM and cardiovascular disease. Lifestyle changes can delay and sometimes prevent the development of DM or cardiovascular disease. MetS has a prevalence of 24% - 78% in the western world (Wang, Q., Chair and Wong, 2017). MetS causes T2DM due to the insulin resistance. Like developing T2DM, MetS is risked by lifestyle or culture, but there are genetic factors that can influence insulin sensitivity and risk. Various professions are predisposing to MetS such as shift work like long distance lorry driving (Canuto, Garcez and Olinto, 2013). Studies suggest a higher prevalence of MetS and its components among shift workers when compared with day workers particularly in regard to lipid and glucose intolerance (Canuto, Garcez and Olinto, 2013).

1.4 Diet

The loss or gain of weight is determined by caloric deficit or surplus respectively. For example, there are sports that enforce weight classes such as professional boxing or Olympic weightlifting. In these sports the subject would target a caloric surplus or deficit in order to gain or lose weight for the specific weight class they are competing in. Individual caloric balance can be determined by calculating total daily energy expenditure (TDEE) and recording calories consumed. A poor diet combined with a lack of exercise will likely result in a calorie surplus and the continued gain of weight and the laying down of fatty tissue in and around abdominal organs (visceral fat). If a professional athlete or an obese patient wanted to calculate TDEE or calories consumed to achieve a target weight they would refer to the amount of energy as for example a daily target to consume 2500 calories. These are kcals or "large calories" and are units of energy. Although the official standardised unit of energy is known as a joule, the commonly used measurement of calories found on food packaging is the kcal which is 1000 calories or a kilocalorie, although usually the labels wrongly say "cal". A kcal (or 4.1868 joules) is the amount of energy needed to raise the temperature of 1 g of water through 1°C at a pressure of one atmosphere, equal to one thousand cal. The calorific value of food is its ability to raise the temperature of 1 g of water when 1g of freeze-dried food is physically burned in a lab experiment. Therefore, it is a measure of energy of food that can be converted to movement, biochemical reactions and the conversion of food to fat. However not all food can be digested to produce energy for example cellulose has a high lab calorie value but low food calorie value (Hargrove, 2006).

A vital part of maintaining a healthy life is eating a healthy balanced diet consisting of eating the right proportions of the macronutrients, carbohydrates, proteins and fats, and the micronutrients, vitamins and minerals. A low-fat diet is recommended to reduce the risk of obesity and coronary heart disease. A high-fat diet will increase fat molecules in the blood which will lead to coronary heart disease. A healthy diet provides the body with a balance of nutrients, including vitamins, minerals and fibre. Nutrition facts labels are mandatory in the UK to allow the population to choose the correct foods for a healthy and balanced diet. A healthy diet should be low in fat, sugar and salt (Berdanier and Berdanier, 2015).

To maintain weight, it is widely but not universally recommended that a patient should eat the same number of calories as TDEE which is known as a calorie balance. A calorie balance will also maintain a patient under or overweight. TDEE is the total number of calories consumed in 24-hours and varies with age and activity levels. To conform with this diet adults should choose low-fat foods when possible to reduce the consumption of fat in the diet as fat has 9 calories per gram compared with protein and carbohydrates which have 4 calories per gram. Reducing the consumption of fat in the diet should reduce the risk of T2DM, obesity and coronary heart disease. Obesity is a result of a person being in a prolonged state of calorie surplus, where a patient will consume more calories than TDEE, combined with a sedentary lifestyle. In order to lose weight, it is essential to be in calorie deficit which is where a person consumes less calories than TDEE. A 24-week study by Redman et al. showed weight loss results using various TDEE calorie restriction diets. Control volunteers who were on a diet of 100% of their TDEE in respect to their calories decreased weight by 1%. Volunteers who were solely on a diet of 75% of their TDEE in respect to their calorie consumption showed a reduction in weight by 10.4%. Volunteers who both restricted diet and increased TDEE were on a diet of 87.5% of their TDEE in respect to their calorie consumption and increased TDEE by 12.5% by using structured exercise showed a reduction in weight by 10% (Redman et al., 2009).

It is now common knowledge that it is recommended to eat five portions of fruit and vegetables a day. The UK Department of Health introduced the five-a-day campaign in 2002. The NHS recommends one portion of fruit or vegetables to be about 80 g or around one handful. The World Health Organisation recommends that individuals consume "a minimum of 400 g of fruit and vegetables per day (excluding potatoes and other starchy tubers)." Sufficient daily consumption could help prevent cardiovascular disease and certain cancers (FAO/WHO, 2005).

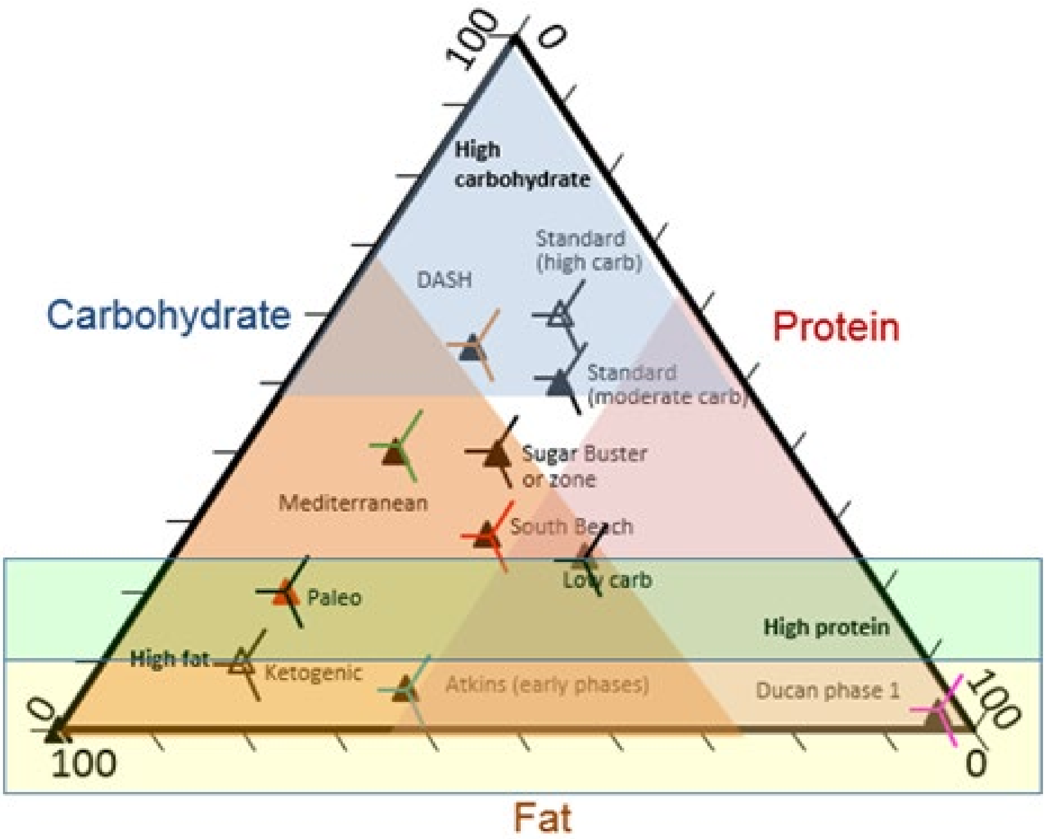

Figure 1, displays the macronutrient ratios for various (unpublished illustration).

1.4.1 The ketogenic diet

In Figure 1 the ketogenic diet is a low-carb (about 10% of calorie intake or less than about 40 g daily), high-fat (about 80%) and optimal-protein (about 20%) diet which is an alternative to the widely accepted standard carb-based diet.

In the UK, the recommendations for normal carb intake are around 45-65%, fat intake recommendation are 20-35% and protein recommendations are 10-35%. Recommending the ketogenic diet to a patient with DM is in theory a viable option as carbohydrates cause greater rise in BG levels compared protein or fat. A ketogenic diet forces the body to metabolise fats rather than carbohydrates. The ketogenic diet will force glycogen stores to be depleted due to low carbs. The three ketone bodies acetoacetate, beta-hydroxybutyrate and acetone are then converted from fatty acids in the liver as an alternate energy source. Protein or fat replaces the lost calories from the lost carbohydrates. A ketogenic diet results in the liver converting fat into fatty acids and ketones. The body then uses ketones as an energy source instead of glucose. A ketogenic diet would need to have between 5 to 25% carbohydrates. Anything above this would supply a surplus glucose load preventing ketosis. Therefore, even a low carbohydrate diet of between 25-38% would still be too much to be defined as ketogenic and approaches Public Health England's Eatwell guide recommendations which the NHS uses (Public Health England, 2016).

A study performed by Goday et al. 2016 concluded that a ketogenic diet was more effective in reducing body weight and improvement of glycaemic control than a standard hypocaloric diet for T2DM patients (Goday et al., 2016). A study by Saslow et al. showed that T2DM patients improved their glycaemic control and lost more weight on a ketogenic diet compared to a conventional low fat diabetes diet online plan (Saslow et al., 2017). These benefits have influenced a common trend across people with an interest in health and fitness to take up this diet. A very strict ketogenic diet is also common treatment among people with epilepsy as ketosis leads to a reduction in the frequency of epileptic seizures, however this is a very low carb diet and must strictly imposed.

However, there are other studies opposing this such as a study by Kosinski where the improvements in obesity and T2DM were limited in time, not totally safe and can be associated with some adverse effects such as insulin resistance (Kosinski and Jornayvaz, 2017).

1.4.2 Atkins diet

The Atkins diet shown in Figure 1 is a low carbohydrate diet written by Robert Atkins released in the 1970s and is very low in carbohydrates and high in fat. It involves around 6% carbs, 59% fat and 35% protein.

1.4.3 Paleo diet

The paleo diet shown in Figure 1 is supposed to be an equivalent diet to what the pre-historic humans consumed during the palaeolithic era including meat, vegetables, fruits, nuts and roots. It refers to the hunter gatherer phase of human evolution. This diet involves no processed foods. It involves 20% carbs, 65% fat and 15% protein.

1.4.4 Pioppi diet

The Pioppi diet is a Mediterranean diet advocated by Dr Aseem Malhotra and caught some media attention in the UK when MP Tom Watson used the diet to lose 44 kg (Saner, 2018). It is based around avoiding added sugar and refined carbs and basing your diet around vegetables and fatty foods. Dr Aseem Malhotra was researching the origins of the Mediterranean diet which lead him to a tiny village in Italy called Pioppi where the average life expectancy for men and women is still 90. He wrote the Pioppi diet to combat the epidemic of misinformation by bringing together evidence to reverse the twin epidemics of obesity and T2DM. The Pioppi diet recommends avoiding all added sugars, fruit juice, honey and syrups and all refined carbs such as bread, rice, pasta, cakes and biscuits. The Pioppi diet also recommends not to avoid saturated fat such as butter, coconut oil, cheese, yoghurt and extra virgin olive oil.

1.5 Carbohydrates

Carbohydrates are the preferred fuel sources for the body when using the glycolytic and oxidative energy systems. There are 2 types of carbohydrates i.e. simple carbohydrates, such as sugar, and complex carbohydrates, such as the starch bread and pasta, that are much slower burning. It is very easy to gain weight by eating excess carbohydrates due to their palatability and the conversion pathway to fat. 1 g of carbohydrates is equal to 4 kilocalories. Carbohydrates should be eaten every day to provide a constant supply of energy. If excess simple carbohydrates are consumed than the body will convert and store as fat. When complex carbohydrates are eaten, they are broken down into glucose and enter the blood stream slowly.

The insulin level peak is lower for an equal quantity of complex carbohydrates than simple carbohydrates because the glucose units are equal, but a metabolic process is needed to break down the complex carbohydrates and this takes time. The delayed effect helps to avoid the carbohydrates stored as fat.

In vertebrates, when food enters the mouth it is physically broken down by chewing using the teeth. Almost all carbohydrates are digested to glucose, other than fibre including cellulose for which humans do not have digestive enzymes. Therefore, most carbohydrates are broken down into smaller polysaccharides by the action of salivary amylase, although salivary amylase is not as active as the pancreatic amylase found in the small intestine. After processing in the mouth, the food passes through the oesophagus by peristaltic contractions into the stomach where the food is turned into chyme. The chyme passes through to the small intestines where it is subjected to digestion mainly by amylase, producing maltotriose and dextrins. Maltotriose is digested by glucosidase to produce glucose molecules. The enzymes mentioned are located at the brush border of the small intestine. This brush border also contains sucrase and lactase which break down sucrose and lactose. The brush border is the microvilli covered surface which increases the surface area of the small intestine to aid the absorption of monosaccharides.

The monosaccharides are absorbed by the intestinal cells and transferred into the bloodstream. Glucose and galactose move into the intestinal cell out of the intestinal lumen by the sodium glucose link transporter, as sodium diffuses down its concentration gradient it brings with it glucose and galactosidase. Monosaccharide transport systems operate by and facilitated transport, systems that allow non diffusible solutes to cross membranes. Common transporters for glucose and fructose are the GLUT receptors. Fructose, another monosaccharide diffuses into the cell via GLUT5, which is a fructose transporter, expressed on the apical border of enterocytes in the small intestine. Once in the intestinal cell the monosaccharides are transferred to the bloodstream via GLUT2 which is a glucose transporter that does not rely on insulin for facilitated diffusion, then once in the bloodstream the monosaccharides can travel to tissue in need of carbohydrates as an energy source. Galactose is phosphorylated and turned into glucose phosphate in the liver.

Beta cells in the pancreas produce the hormone insulin and store it inside granules within the cells. Beta cells are sensitive to the amount of glucose in the blood stream because of GLUT2 receptors on the beta cell membrane. Beta cells react to BG levels constantly and detect how much insulin it should release to combat BG levels. When a person eats something high in carbohydrates such as rice the glucose level in the blood rises and the beta cells trigger the pancreas to release insulin into the bloodstream. When glucose enters the cell via the GLUT2 receptor potassium and calcium gateways exclude potassium and cause calcium to enter the cell. This trigger the release of insulin from the granules shown in Figure 2, leaving the cell and entering the bloodstream from where it transports around the body and binds to skeletal muscle and adipocytes which open the cell doors to let the glucose in. The cells then either metabolise glucose, generating a source of ATP or store it as glycogen for later use.

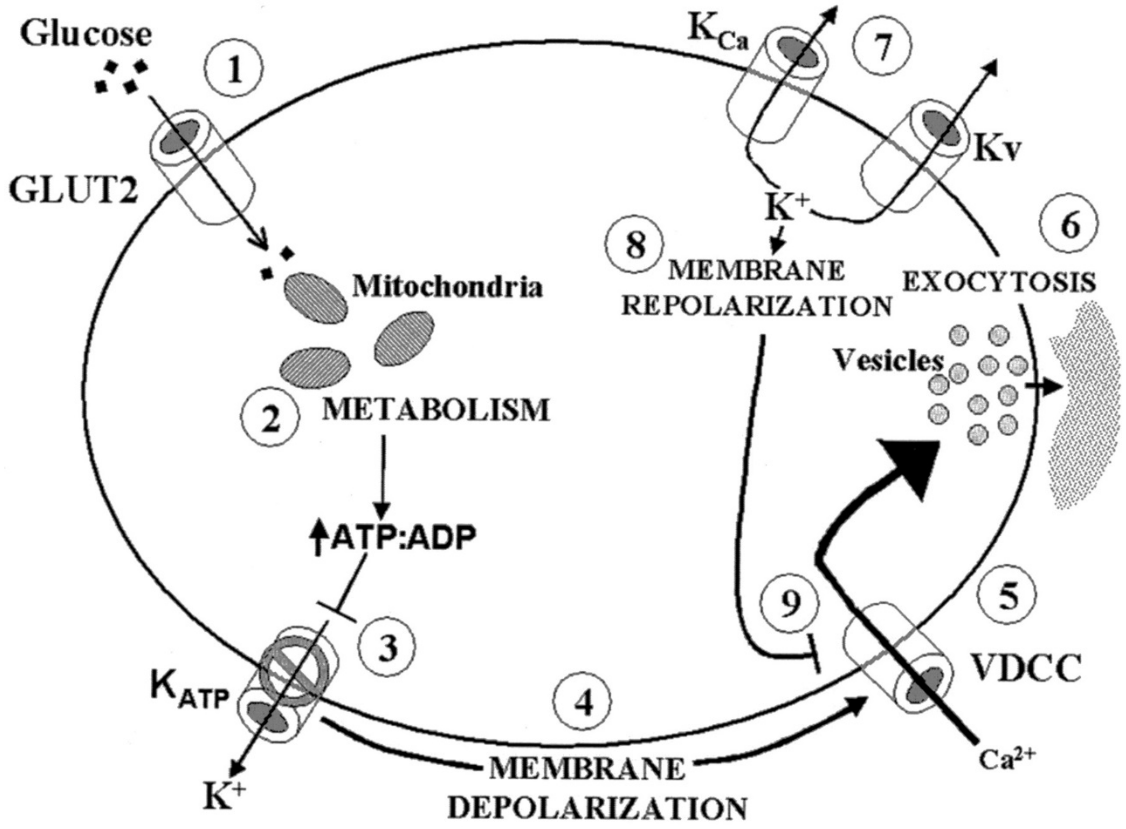

Figure 2, displays a model of the beta cell found in Macdonald (MacDonald et al., 2002).

Guidelines recommend eating a diet with a high intake of fibre rich food including fruit. This is based on the many positive effects of fruit on human health, however there are concerns that fruit intake has a negative impact on glycaemic control, due to high levels of sugar, and therefore recommend restricting high fruit intake.

Although T2DM is preventable it is still possible to have a predisposition for example people of South Asian ancestry are at up to 4 times more at risk of T2DM compared to European populations (Kooner et al., 2011). This may be a genetic protection against low food supply. Studies revealed that by age 80, twice as many British South Asian, Black African and African

Caribbean men and women had developed diabetes compared with Europeans of the same age (Tillin et al., 2012). A person from these communities should be screened for diabetes earlier than the general population, from the age of 25 rather than 40. Whilst it is important for everyone to maintain a healthy weight, it is even more important for people from these communities to avoid being overweight.

If a person is at a genetic predisposition to developing T2DM it is recommended to adapt the diet to accommodate for this, for example eating 9 fruit and vegetables a day instead of 5 a day. Unfortunately, the older generation may find it difficult to change habits, but it is important to adjust their diet accordingly and exercise more frequently to encourage and support positive change.

1.6 Proteins

Proteins vary in size from tens to several thousand amino acids. There are 4 levels of distinct protein structures of which the primary structure indicates the amino acid content. Amino acids can be metabolised into fuel. Most amino acids are solely glucogenic, two are solely ketogenic and a few are both ketogenic and glucogenic. Lysine and leucine are exclusively ketogenic amino acids. The five amino acids that are both ketogenic and glucogenic are phenylamine, isoleucine, threonine, tryptophan and tyrosine. The remaining 13 amino acids are exclusively glucogenic. Proteins are usually used to build up and repair structural and functional proteins such as cell structure, enzymes, muscle tissue and haemoglobin, however when included in a diet they produce ketones. The protein structures in foods consist of amino acids of which nine are essential to include in the diet because the body does not synthesize them. There are 20 amino acids in total and not all proteins contain all of them. In terms of energy value, 1 g of protein is equal to 4 kilocalories. The body uses protein to repair and grow. Protein is only used for energy when the body has insufficient carbohydrates. In a ketogenic diet high protein is useful for producing ketones as fuel but in a hyperglycaemic ketosis crisis, the absence of glucose means the muscles are broken down and the patient loses weight and becomes dangerously ketotic. In controlled diabetes a ketogenic diet is not dangerous.

1.7 Lipids

Lipids are the most energy dense of the three macro nutrients. Lipids contain fatty acids which can be categorised into three main groups of saturated fats, polyunsaturated fats and monounsaturated fats. 1 g of fat is equal to 9 kilocalories. Fats are a concentrated source of energy, therefore suitable for energy reserve which is used in the oxidative system. Fats are required for the production of cell membranes and hormone metabolism but also keep the body warm and protect the skeleton and organs.

1.8 Type 2 diabetes mellitus

T2DM has rapidly become an epidemic in the UK. The UK's National Health Service (NHS) spent £10.3billion on diabetes in 2015, 10% of the total NHS budget (Cannell, 2016). The current cost of direct patient care including treatment, intervention and complications is estimated at £8.8 billion but it is estimated that the direct cost will increase to £15.1 billion in the next 25 years which makes 17% of the NHS budget (Diabetes UK, 25/04/2012).

The current indirect costs associated with diabetes, such as those related to increased death and illness, work loss and the need for informal care are estimated at £13 billion but it is estimated that the indirect cost of diabetes will increase to £20.5 billion in the next 25 years.

If the rise in diabetes continues at the current rate it is said that the NHS will not be able to afford the cost of treatment in the future.

Therefore, it is essential to prevent T2DM. It is important to prioritise the prevention rather than treatment. Unlike T1DM many cases of T2DM are preventable even if a patient has a predisposition to T2DM such as South Asians. Nevertheless, prevention is not easy as patients become accustomed to the modern sedentary lifestyle and bad eating habits. In order to tackle the problem the development of the disease needs greater understanding.

1.9 Insulin resistance

Insulin resistance is one of the main metabolic signs of T2DM. Insulin resistance can be defined as a condition in which cells fail to respond normally to the hormone insulin in liver muscle and fat tissue. When the body produces insulin under insulin resistance, the cells are resistant to the insulin and are unable to use it as effectively, leading to high BG. Subsequently beta cells in the pancreas increase mass and production to reduce BG levels, this fails to work and contributes to high blood insulin levels (hyperinsulinemia) (Freeman, Soman-Faulkner and Pennings, 2019). Hyperinsulinemia is associated with high blood pressure, heart disease and obesity.

Chronic insulin resistance progresses to T2DM when beta-cells are unable to produce sufficient insulin to compensate for decreased insulin sensitivity (Fu, Gilbert and Liu, 2013).

Insulin resistance leads to decreased glucose uptake by peripheral tissue predominantly the muscles and an increase in hepatic glucose production known as gluconeogenesis GNG (Meah and Juneja, 2015). This may be a result of the increasing lack of exercise and increasing unhealthy foods in the modern lifestyle.

Chronic overnutrition that creates chronic hyperglycaemia can gradually induce insulin resistance and insulin secretion impairment induced gradually and mainly by high BG, genetic predisposition, obesity and physical inactivity (Yan, 2014).

Although chronic insulin resistance is harmful, acute insulin resistance is thought to be a self-defence mechanism. It has been proposed that evolutionary pressure to preserve glucose for use by the brain during starvation leads to a genetic propensity towards insulin resistance in peripheral tissues (Wang, G., 2014).

Physical activity greatly improves insulin sensitivity. Combining aerobic activities, such as walking, swimming and cycling, with resistance activities, such as weight training has the most significant effect on insulin sensitivity although any type of physical activity will improve the insulin's effectiveness. When the body burns glucose during exercise glycogen stores will deplete. After exercise glycogen stores replenish using glucose from the bloodstream, the effectiveness of which depends on the sensitivity to insulin which in turn improves the more exercise is done.

As the pancreas can increase insulin production, insulin resistance alone will not have any symptoms at first, other than a high insulin level. However, over time as insulin resistance worsens and the activity of the beta cells will increase which can exhaust them. Eventually the pancreas can no longer produce enough insulin to counteract the glucose in the blood which results in hyperglycaemia and ultimately T2DM.

Exercise promotes glucose clearance by increasing skeletal muscle GLUT4 (Glucose transporter 4)-mediated glucose uptake.

More importantly exercise upregulates muscle GLUT4 expression in an insulin-independent manner under conditions of insulin resistance, such as with T2DM (Gurley et al., 2016).

1.10 Type 1 diabetes mellitus

Although T1DM and T2DM share many symptoms, they have different causes. T1DM occurs due to an auto-immune progressive destruction of pancreatic beta cells by cd4+ and cd8+ t cells and macrophages infiltrating the islets (Yoon and Jun, 2005). The destruction is practically total which means a loss of normal BG control. Insulin must be administered to regulate BG levels. The patient must learn to self-inject or use a continuous BG monitor or insulin pump. The onset of T1DM commonly occurs before adulthood but can also appear during adulthood.

1.11 LADA (Latent autoimmune diabetes of adulthood)

Latent autoimmune diabetes of adulthood is a form of T1DM that occurs in adulthood. It occurs more slowly than T1DM which is usually diagnosed during childhood. Therefore, LADA often gets mistaken for T2DM due to the late onset in relation to the majority of T1DM cases. The frequent urination and excessive thirst caused by hyperglycaemia is experienced by the patient when onset occurs, but the progression may not be noticed until a crisis point in wellbeing.

1.12 Gestational diabetes mellitus

GDM is diagnosed when a woman without previous DM develops high BG levels during pregnancy. GDM is caused by not enough insulin combined with insulin resistance. Babies born to mothers with uncontrolled BG levels are at an increased risk of having low BG after birth, being overweight after birth and jaundice. If untreated it can also result in a stillbirth. Mackins study showed that mothers with T2DM were at least 4 times likely to deliver a stillborn child whist those with T1DM were more than three times likely (Mackin et al., 2019). As the baby gets older it will have a higher risk of being overweight and developing T2DM. GDM usually resolves after the baby is born although the mother is at increased risk of developing T2DM. Risk factors include being overweight, previously having T2DM, family history of T2DM and having polycystic ovarian syndrome. Diagnosis is usually undertaken with an oral glucose tolerance test because the usual test, a HbA1c test, is based on the previous 3-month period and not current levels therefore may not reflect pregnancy changes. Prevention such as maintaining a healthy weight and to exercise regularly before pregnancy is essential to reduce the risk of GDM. GDM is treated with a change in diet, exercise and possibly insulin injections. GDM affects 3 to 9% of pregnancies worldwide (Donovan and Mcintyre, 2010). GDM is more common in the third trimester of pregnancy.

1.13 MODY (Maturity onset diabetes of young)

Maturity onset diabetes of the young (MODY) is caused by a mutation in a single gene. MODY runs strongly in families. If a parent has this gene mutation their offspring will have a 50% chance of inheritance. The most common genes that cause MODY are HNF1-alpha, HNF4-alpha, HNF1-beta and glucokinase. The identification of an HNF-1 alpha gene mutation in a patient with T2DM confirms the diagnosis of MODY (Ellard, 2000).

1.14 Prevalence of diabetes

In high income countries, approximately 87 to 91% of all people with diabetes are estimated to have T2DM whilst 7 to 12% are estimated to have T1DM (International Diabetes Federation, 2017). Along with the 415 million adults who are estimated to currently have diabetes 318 million 20 to 79 year olds have impaired glucose tolerance which is expected to increase to 481 million in 2040 (International Diabetes Federation, 2017).

It has been said that the NHS will not be able to afford the cost of treatment in the not very distant future, therefore it is vital that diabetes is prevented. Structured exercise programmes are very effective methods of prevention but also treatment. The cost of diabetes today from the NHS is an estimated £14 billion a year or 10% of their budget (Diabetes.co.uk, 2018).

It is estimated that the are 3.8 million adults with T2DM in the UK, However there are also estimates of 4.7 million (Diabetes UK, 2018b). 56% of all adults with diabetes are male whilst 44% are female (Diabetes UK, 2012). Diabetes UK estimates that six million people across the UK are at increased risk of T2DM with a HbA1c between 6.0 to 6.4 (Diabetes UK, 2016). In the last five years prescriptions for T2DM have increased a third from 26 to 35 million a year according to NHS data (BBC, 2016).

1.15 Causes of T2DM

In the second half of the 20th century there was a mass increase of processed foods preservatives, added sugar in foods and ready meals. This combined with the sedentary lifestyle increasing due to low labour-intensive work in offices, prolonged television watching and the introduction of cars in western culture have caused a decrease in physical activity. This increases the risk of gaining weight and becoming T2DM. Men who watch television more than 40 hours a week have nearly threefold increase in the risk of T2 diabetes compared with those who spend less than one hour a week watching television (Hu, F. B. et al., 2003). Sedentary behaviour is a key risk factor that can increase the risk of metabolic disease (Vancampfort et al., 2017). All causes of T2DM are preventable but age and genes are also a factor. Unfortunately, all the causes are lifestyles and habits which are very hard to change in people who are stuck in a routine and stubborn about change.

In a study of French adults 45 years or older, a 10% increase in the proportion of highly-processed food with many additives and multiple processes (sometimes known as ultra-processed) consumption was statistically significantly associated with a 14% high risk of all-cause mortality, therefore an increase in ultra-processed food consumption may be associated with an overall higher mortality risk (Schnabel et al., 2019).

The increasingly unhealthy modern western lifestyle of sugary meals combined with lack of exercise has increased the rate of T2DM. As the sedentary lifestyle is more prevalent in the more economically developed countries than less economically developed countries it would be expected that there is a higher prevalence of T2DM, which is the case (Hu, Frank B., 2011). T2DM is generally assumed to affect older people and it even used to be called 'mature onset' diabetes. However, T2DM is becoming more prevalent in younger people, around 100 under-10s are now diagnosed each year. The youngest case was a 3-year-old in Texas (Knapton,). There have been many cases of childhood T2DM in the USA prior to the UK. Since the first case of childhood T2DM in Birmingham was diagnosed in 1993 there have been 17 recorded cases of children with T2DM (Fagot-Campagna, Narayan and Imperatore, 2001).

The body's ability to metabolise food slows down with age. In middle age the level of several hormones such as oestrogen, testosterone and growth hormones begin to drop. The body starts to lose lean muscle roughly 6 ½ lbs of muscle each decade. Less muscle means the body burns fewer calories therefore requiring less fuel. The reason the metabolism slows down with age is the number of mitochondria in the body's cells start to reduce with age. These are the body's "power plants". Mitochondria combine nutrients from the diet with oxygen from the lungs (Krebs cycle) to release energy. As the number of mitochondria in the body reduces the ability to metabolise fat as efficiently is lost. Excess carbohydrates get converted by glycolysis into glycerol and fatty acids which are combined to form excess visceral fat. Visceral fat surrounds the organs and creates signally against that promote inflammatory adipokines throughout the body. Too many calories and a drop in metabolic rate can be a lethal combination, fat is much more than an inch on the waistline, but spreads throughout the entire body in almost every available space especially in the abdomen. Yellow visceral fat deposits attach onto the internal organs and inside the blood vessels where deposits build up on the inner walls to cause atherosclerosis. The heart then works harder to pump blood through the restricted vessels. In extreme cases fat can block the vessels completely and if this happens the result can be fatal. The heart muscles are deprived of oxygen and nutrients, muscles risks going into spasm causing a heart attack. Eating the same amount of food into adulthood after the body has changed with age to require less would create a surplus. The excess food gets converted into fat. For women, fat tends to go to their hips which stores a steady energy supply for pregnancy but is maintained long after that stage. Men store fat in a different area, inside the abdomen cavity but this is internal visceral fat which causes a "pot belly" or "beer belly". This evolved for quick energy release it helped sustain our male ancestors during hunting trips which acts as an extra battery using the oxidative energy system.

Mitochondria generate most of the cell's supply of ATP. Each cell type can have a varied number of mitochondria present for example a red blood cell has no mitochondria whereas the liver 20 to 25% of the cytoplasmic space is taken up by mitochondria with 1000 to 2000 mitochondria per cell. The mitochondria also has a role of regulating cellular metabolism. A relative or total absence of mitochondria is a fatal inborn metabolic disease.

ATP is the currency of the cell. ATP production is achieved through the phosphorylation of ADP, through respiration and its production consists of a central set of reactions known as the Krebs cycle and the electron transport chain. The inner membrane of the mitochondria has a large number of intermembrane proteins used for the production of ATP. Glucose pyruvate and NADH are oxidised and produced in the cytosol. This cellular respiration known as aerobic respiration is dependent on the presence of oxygen. When oxygen is in short supply the glycolytic products will be metabolised by anaerobic fermentation a process that is independent of the mitochondria. The production of ATP from glucose is a lot more efficient during aerobic respiration compared to anaerobic fermentation.

Glucose generates ATP over three separate stages glycolysis, the Krebs cycle and the electron transport chain. Fructose is almost the same process as glucose but bypasses the glycolysis stage and heads straight to the pyruvate stage.

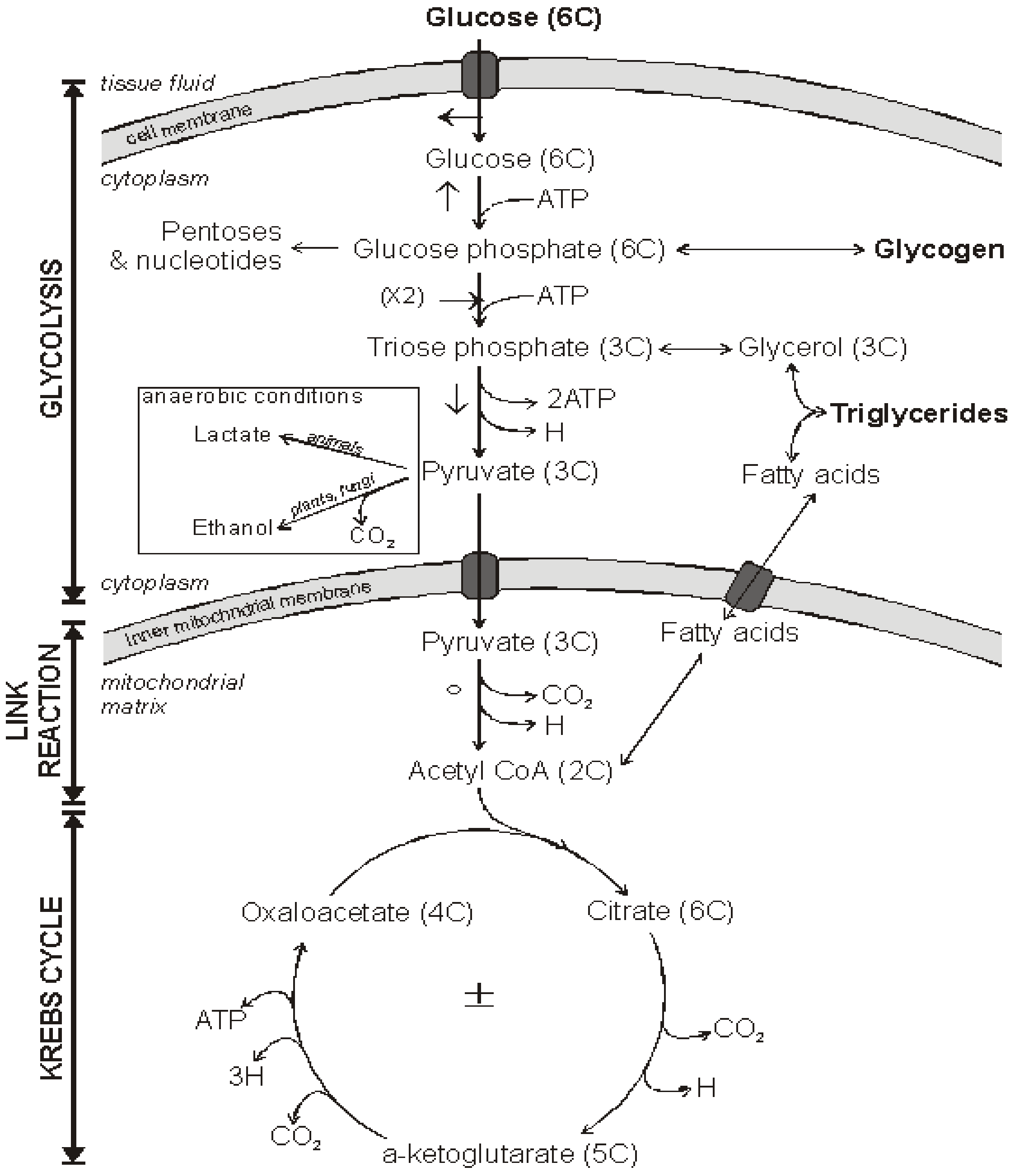

Figure 3, displays the overview of aerobic respiration (Learnwise, 2019).

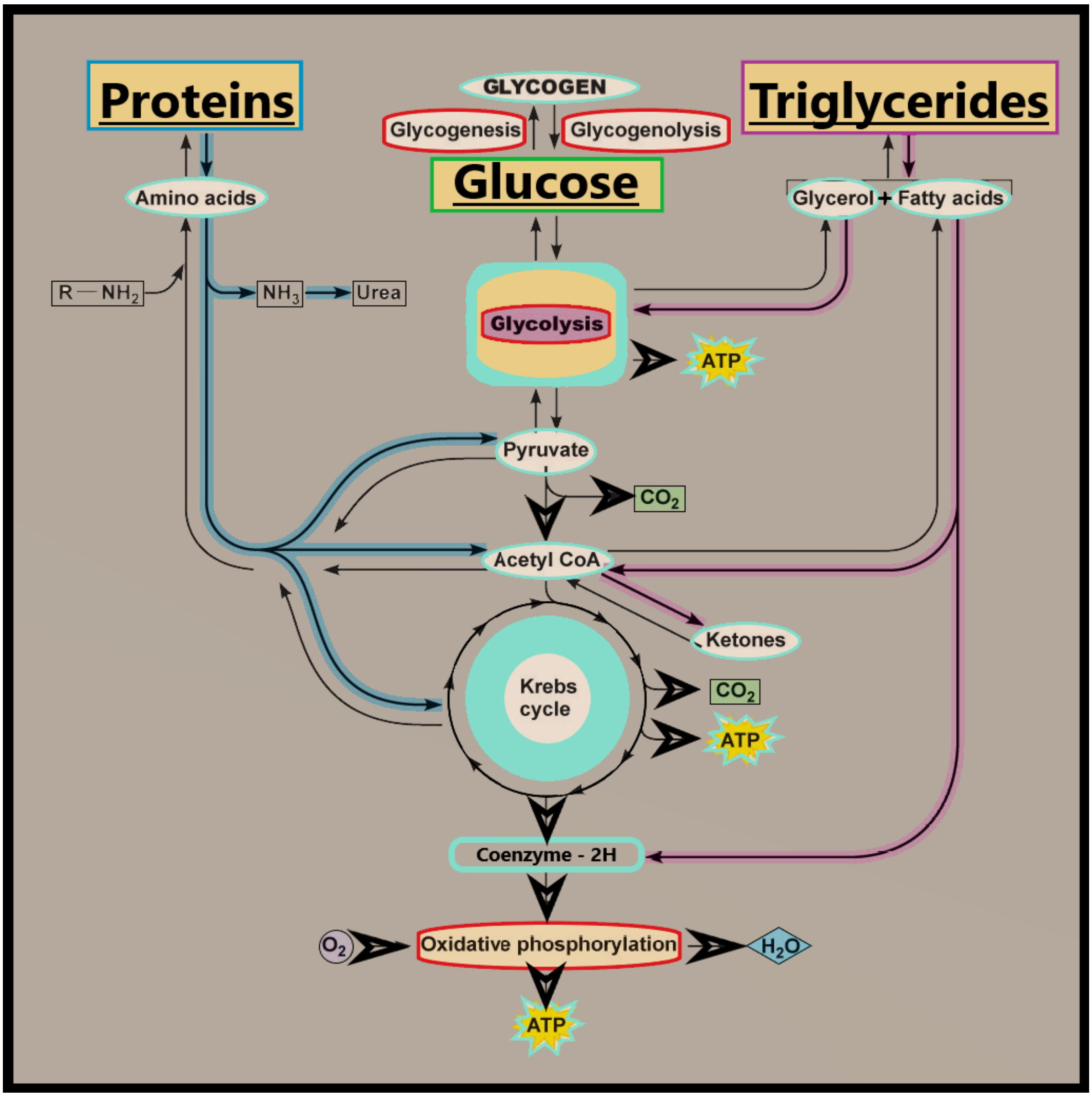

Figure 4, displays the catabolism of glucose, lipids and amino acids. (unpublished illustration)

The first part of respiration is glycolysis. Glycolysis is the breaking down of glucose into pyruvate and is described as anaerobic respiration whilst the Krebs cycle and the electron transport chain are aerobic. Glycolysis takes place within the cytoplasm of the cells and is the breaking up of glucoses 6 carbon rings into two 3 carbon molecules called pyruvate. Pyruvate can also be converted back to glucose by reversing glycolysis which is called gluconeogenesis. Glycolysis produces 2 molecules of ATP per molecule of glucose. In the presence of oxygen pyruvate enters the mitochondrial matrix to proceed with aerobic respiration but in the absence of oxygen it is converted to lactate. Lactate stores a lot of energy and when oxygen is available it is converted back to pyruvate.

The next step in cellular respiration after glycolysis comes the Krebs cycle which happens across the inner membrane of the mitochondria but before the Krebs cycle can start, the pyruvate produced from glycolysis is oxidised. One of the carbons off the 3 carbon chain from the pyruvate bonds with an oxygen molecule and leaves the cell as CO_2. What is left is a 2-carbon compound called acetyl coenzyme A, this is called the link reaction. The acetyl coenzyme A then enters the Krebs cycle, named after Sir Hans Krebs who discovered the Krebs cycle at Leeds University in the 1940's. The 2-carbon acetyl is transferred from acetyl coenzyme A to the 4-carbon oxaloacetate to form the 6-carbon citrate. Citrate is then broken down in several steps to re-form oxaloacetate, producing carbon dioxide and hydrogen in the process. The CO_2 diffuses out the cell and hydrogen is bonded to NAD or by an alternative hydrogen carrier called FAD. These hydrogens are carried to the inner mitochondrial membrane for the final part of respiration.

Finally comes the electron transport chain which takes place within the inner mitochondrial membrane, using integral membrane proteins. These proteins from four trans membrane complexes called complexes 1,2,3 and 4. These complexes contain around 40 individual polypeptide chains which undergo many functions such as enzymes and trans-membrane pumps. In the electron transport chain the hydrogen atoms from NADH gradually release the energy to form ATP and are finally combined with oxygen to form water. NADH molecules are bound to complex 1 and release their hydrogen atoms as protons and electrons. The NAD molecules then return to the Krebs cycle to collect more hydrogen, whereas with FADH it binds to complex 2 rather than complex 1 to release its hydrogen. The electrons are passed down the chain of proteins complexes from 1 to 4, each complex binding electrons more tightly than the previous one. The electrons give up some of their energy in complexes 1,2 and 4 which is then used to pump protons across the inner mitochondrial membrane by active transport through the complexes. In total 10 protons are pumped across the membrane for every hydrogen from NADH whereas with FADH it is 6 protons that are pumped across the membrane. In complex 4, 4 electrons and 4 protons (equals 2 hydrogen atoms) are combined with molecular oxygen (O_2) to form 2 molecules of water. The oxygen has diffused in from the tissue fluid, crossing the cell and mitochondrial membranes by lipid diffusion. The energy of the electrons is now stored in the form of a proton gradient across the inner mitochondrial membrane. The energy gradient can be used to generate ATP in the ATP synthase enzyme. The ATP synthase enzyme has a proton channel through it and as the protons "fall down" this channel their energy is used to make ATP, spinning the globular head as they go. It takes 4 protons to synthesize 1 ATP molecule.

When the liver is overwhelmed with cholesterol, cholesterol rich plaque builds up in the arteries which is known as atherosclerosis. Diabetes, by driving inflammation and slowing blood flow, accelerates atherosclerosis where cytokines such as Il-6, Il-17a and TNFα are responsible for triggering the inflammatory cascade. These stimuli promote abnormal attachment of leukocytes, such as monocytes and T-lymphocytes to the endothelial cells that lie in the artery lumen. Once inside the artery wall monocytes differentiate into macrophages secreting Il-6 and TNFα. These macrophages go on to form lipid rich foam cells. Il-17a is produced by T cells and aids in the recruitment of monocytes to the inflammation site continuing the process of inflammation and plaque build-up. As plaque builds up over time it can become unstable and vulnerable to rupture if the wall of the artery surrounding the plaque becomes weak and rupture. Blood clotting components interact with the substances of the plaque triggering a clot which may block the entire artery and causing heart attacks, strokes etc. This process however can be prevented by long term control of food intake that promotes diabetic improvement.

In healthy coronary arteries blood flows without obstruction but in diseased coronary arteries the plaque bulges out into the path of the onrushing blood blocking the oxygen and nutrients the heart desperately needs and from time to time causing symptoms like chest pains and shortness of breath, but heart attacks also result from plaque that does not protrude into the artery itself and remains hidden in the artery wall causing no restriction on blood flow thus no symptoms. This is because the wall structure can suddenly rupture, causing a blood clot to form therefore blocking blood flow and resulting in myocardial infarction.

The visceral fat surrounding the organs in the abdomen is insidiously toxic. The toxicity of visceral fat interferes with the signal or sends the wrong signal failing to communicate to the brain that the stomach is full, allowing the individual to continue eating excess food, gain more weight and worsening their situation in a downhill spiralling effect. Toxic visceral fat encircles organs and increases inflammation, secretes toxic chemicals that increases inflammation through body. Abdominal fat increases production of IL-6 which increases further inflammation throughout the body, metabolism is being governed by excess fat and adiponectin tells body to store more visceral fat. This leads to a viscous cycle which leads to plaque build-up in arteries. Atherosclerosis effects cardiovascular system and increases blood pressure overtime.

1.16 Diagnosis tests for diabetes mellitus

There are various diagnosis methods for DM. The 4 most used are the HbA1c test, Oral glucose tolerance test, fasting BG test and the random BG monitoring test.

1.16.1 HbA1c

HbA1c analysis is the most accurate standard of diagnosis of blood glycaemic control (Zemlin et al., 2011). HbA1c is the average BG reading over the past 90 days as this Is the life cycle of erythrocytes. Erythrocytes are where the globular proteins haemoglobin are located. A blood sample is usually taken but a finger prick test is possible, The HbA1c test replaced the OGTT as the standard diagnosis test as there is no need for the patient to fast, and reflects recent prevailing blood sugars and therefore no-one with raised BG should be missed. A HbA1c level of 48mmol/mol (6.5%) or above indicates a person has DM. A HbA1c level of 42-47mmol/mol (6.0–6.4%) indicates pre-diabetes or impaired glucose tolerance. A HbA1c below 42 mmol/mol (6.0%) indicates no DM is present (NICE, 2012).

1.16.2 Oral glucose tolerance test (OGTT)

This test is often used to determine whether a patient has gestational diabetes. Unlike the HbA1c test, the results of an OGTT are current. An OGTT determines whether a patient has T2DM by consuming 75 g of sugar after a 10-12 hour fasted state and measuring their BG concentrations every 10 minutes over a 2-hour period. FBG and PPBG are taken before and after an OGTT.

1.16.3 Fasting blood glucose test

The FBG level is the BG concentration level taken after 10-12 hours of fasting, this is usually measured in the morning for convenience and is very often taken at the start of a fasted OGTT. An FBG concentration above 7.0 mmol/l is the indicates DM whilst an FBG level between 5.5-6.9 mmol/l indicates pre-diabetes or impaired glucose tolerance. A normal FBG is 3.9-5.4 mmol/l (NICE, 2012).

1.16.4 Post-prandial blood glucose level (PPBG)

The PPBG is a BG test that identifies the BG levels 2 hours after a meal. If the pancreas is functioning correctly the BG levels should normalise after a meal to suitable levels. A 2-hour PPBG level of above 11.1 mmol/L is diagnosis test for T2DM (World Health Organisation, 2019). A PPBG level above 7.8 mmol/L is impaired glucose tolerance (World Health Organisation, 2006).

1.16.5 Random blood glucose monitoring test

A random BG concentration test is an ordinary finger prick test that is an everyday occurrence for T1DMs. If the reading is above 11.1 mmol/L this indicates a person has diabetes mellitus (World Health Organisation, 2019).

1.17 Insulin sensitivity test

This insulin sensitivity test is not a specific diagnostic test for T2DM but measures the body's sensitivity to insulin, Blood samples are taken at specific time points and identify insulin sensitivity by using the Matsuda index (Matsuda and DeFronzo, 1999). This can be performed at the same time as an OGTT.

1.18 Treatment

1.18.1 Lifestyle changes

Lifestyle changes generally include dietary changes, physical activity changes and stopping smoking. Physical activity increases mitochondrial content in muscle. Mitochondrial biogenesis can be defined as the growth and division of pre-existing mitochondria. which increases glucose uptake by the cell. The basis for recommending exercise for treatment of

T2DM is the common knowledge that muscle contraction increases glucose uptake in skeletal muscle (Hayashi, Wojtaszewski and Goodyear, 1997; Holloszy and Hansen, 1996; Lund et al., 1995; Wallberg-Henriksson and Holloszy, 1985; Wallberg-Henriksson et al., 1988). Studies have indicated that in T2DM the mitochondria are relatively dysfunctional causing mitochondrial biogenesis to decrease (Bonnard et al., 2007; Cheng and Almeida, 2014). Therefore, exercise may well work positively to reverse this. Exercise has been shown to change DNA methylation to favour gene expression responsible for mitochondrial biogenesis and function (Cheng and Almeida, 2014).

More importantly exercise upregulates muscle GLUT4 expression in an insulin-independent manner under conditions of insulin resistance, such as with type 2 diabetes (Gurley et al., 2016). Different aspects of diabetes respond differently to particular exercise styles, so for example low intensity exercise is essential to burn the visceral fat which must be targeted as fuel during exercise. Prolonged activity that predominantly uses the oxidative energy system would be most effective in burning visceral fat as the ATP-PC and glycolytic system do not burn fat as fuel. Metformin is also a good method to increase fat burning as it essentially blocks the production of ATP therefore causing the next energy system to become predominant. There are also good reasons to perform cardiovascular and resistance components. Therefore, structured exercise programmes are an ideal and cost-effective method of prevention but also treatment.

Alongside exercise the best programmes will contain dietary advice for example, isocaloric low-carb low-fat calorie restricted diets were effective on weight loss in patients with T2DM (Kirk et al., 2008). Substitution of carbohydrates with monounsaturated fatty acids may be associated with lower mortality risk and weight reduction (Campmans-Kuijpers et al., 2016).

In Lim et al. showed that reversal of T2DM with normalisation of beta cell function was associated with decreased pancreas and liver triacylglycerol. It was shown that over 8 weeks of dietary restriction the beta cell function normalised as pancreatic fat decreased. The conclusion was that insulin secretion and resistance in T2DM had a common cause and was linked to visceral fat deposition. The important dietary component was to restrict saturated fat (Lim, E. L. et al., 2011). Therefore, the move towards high fat ketogenic diets might therefore need modification to ensure that the fat is unsaturated.

1.18.2 Oral medication

1.18.2a Metformin

Metformin is the most widely prescribed drug in the UK for T2DM because it reduces HbA1c and body weight. Schweizer et al. found that after 1 year of metformin HbA1c levels decreased by 1.4% and weight reduced by 1.4 kg most of the Hba1c reduction was attained by 12 weeks (Schweizer et al., 2007).

Metformin is a biguanide that works by decreasing gluconeogenesis and by increasing peripheral utilisation of glucose. It only acts in the presence of endogenous insulin therefore it is only effective if there are residual functioning pancreatic islet cells.

Metformin also dramatically increased the amount of symbiotic butyrate-producing microbes in the gut. The changes are sudden that people usually get diarrhoea when they first start metformin and must slowly titrate up their dose from 500 mg a day to around 2000 mg. This side effect can be reduced by feeding the gut microbes by an appropriate diet containing probiotic food such as resistant starches. Some of the metformin's effects on glucose metabolism are due to its effect on gut microbes.

However, a recent study performed by Moore et al. reported that individuals with T2DM or impaired glucose tolerance performed less well on cognitive tests when using metformin than those managing diabetes with other approaches (Moore et al., 2013).

Metformin mainly functions as a weak inhibitor in mitochondria. With the cell unable to generate normal quantities ATP, there is an upregulation of beta oxidation and related enzymes. Metformin essentially forces fat/ketone metabolism in the face of abundant glucose supply. From a macro view, myocytes quickly burn off whatever local triglycerides they have left, as they are starved of energy unable to utilize glucose. Cells then become more insulin sensitive once depleted of local triglyceride stores. This is all very good from an oxidative stress or cell survival standpoint.

1.18.2b Sulphonylurea

Sulphonylureas provokes the pancreas into producing more insulin and increases the effectiveness therefore some residual activity of the pancreatic beta cells must be present (Szablewski, 2011). The requirement of present pancreatic beta cells makes sulphonylureas unsuitable for treatment of T1DM but suitable for T2DM. Hypoglycaemia and weight gain are side effects.

1.18.2c Dipeptidyl peptidase-4 (DPP-4) inhibitors

DPP-4 inhibitors, sometimes referred to as gliptins, help stimulate the production of insulin and reduce the production of glucagon, particularly during digestion. DPP-4 inhibitors work by inhibition of the enzyme that metabolises GLP-1. Usually prescribed for people who have not responded well to drugs such as metformin and sulphonylureas. Gliptins are significantly associated with an 18% decreased risk of all-cause mortality, a 14% decreased risk of heart failure and no significant change in risk of cardiovascular disease. Dual treatment with gliptins and metformin associated with decreased risk of all three outcomes, 38% heart failure, 33% cardiovascular disease 48% for all-cause mortality (Hippisley-Cox and Coupland, 2016).

1.18.2d Alpha-glucosidase inhibitors (AGI)

AGI slows down the indigestion of carbohydrates in the small intestine and therefore can help reduce after meal BG levels (Joint Formulary Committee, September 2018).

1.18.2e Glucagon like peptide-1 (GLP-1) agonists

Exanitide, liraglutide and lixisenatide bind to and activate the GLP-1 receptor to increase insulin secretion, supress glucagon secretion and slow gastric emptying. This is an injectable treatment for T2DM, they are often prescribed to people for whom traditional treatments have been unsuitable (Joint Formulary Committee, September 2018).

1.18.2f Sodium glucose co-transporter 2 (SGLT2) inhibitors

SGLT2 inhibitors are taken once a day with or without food to help the kidneys lower BG levels. SGLT2 inhibitors work by preventing the reuptake of glucose forcing glucose to be excreted in the urine. This oral medication was approved for treatment in T2DM in 2013 (Joint Formulary Committee, September 2018).

1.18.2g Meglitinide

Meglitinides stimulate insulin production in the same way as sulphonylureas. Meglitinides are for patients with T2DM and are required to be taken before eating. The short acting nature of meglitinides mean side effects common with sulphonylureas are less likely.

1.18.2h Thiazolidinedione (Glitazones)

Thiazolidinedione, or commonly known as glitazones, reduce BG levels by increasing the effectiveness of insulin by decreasing insulin resistance. If the side effect of weight gain occurs DPP-4 inhibitor may be a more suitable treatment. Glitazones also help lower blood pressure and triglyceride levels.

1.18.3 Insulin

About 90% of people with DM have T2DM. Although almost all T1DM inject and only some T2DM inject there are still more total T2DM injectors than T1DM injectors due to the vast numbers of T2DM.

There are various types of insulin. Analogue insulin is a subgroup of human insulin, being laboratory biosynthesised and genetically altered to create either a more rapid acting or more uniformly acting form of the insulin. There are short acting, intermediate acting and long acting insulins available.

1.18.4 Adjunct Treatment

Most T2DM are late being diagnosed and usually experience metabolic syndrome symptoms that increase their risk of complications. These symptoms are high blood pressure, high blood lipids and obesity. Therefore, apart from glucose control treatment consists of addressing these other disorders to prolong and increase the quality of life.

1.18.4a Angiotensin converting enzyme ACE inhibitors

ACE inhibitors reduce the activity of angiotensin converting enzyme which is responsible for hormones that control blood pressure. Angiotensin has a narrowing effect on blood vessels which increases blood pressure. By inhibiting this enzyme, the blood vessels relax and widen, which lowers blood pressure.

1.18.4b Beta-blockers

Beta-blockers work by making the heart beat more slowly and with less force, thereby reducing blood pressure. Beta-blockers block the effects of adrenaline on the beta receptors of blood vessels and the heart. This approach to controlling blood pressure is much less popular than it used to be.

1.18.4c Statins

Statins block the pathway for synthesizing cholesterol in the liver. As most cholesterol comes from production in the liver and not through diet, blocking this causes cholesterol in the blood to fall. As low-density lipoproteins can lead to an atherosclerosis and cardiovascular disease (CVD) these risks are reduced by including statins in the medication.

1.18.5 Problems with treatments

The problem with many of the most commonly used treatments such as metformin tablets is that they themselves cause side effects such as with the liver function and with memory, for example. Therefore, a preferable effective treatment without side effects is to improve diet and increase exercise unless the illness has become too advanced to treat conservatively. Treatment with insulin is not straightforward because it may increase insulin resistance and may contribute to obesity whereas the aim should be to reduce insulin resistance. Sulphunureas and other secretagogues provoke insulin output which increases weight in the same way as insulin therapy.

1.18.6 Treatments in development

De Montfort University has been developing an artificial pancreas (Taylor et al., 2016). It is a closed loop device that dispenses insulin into the body in response to glycaemic changes. This artificial pancreas aims to combine the functions of BG monitors and insulin pumps and adjust insulin appropriately and continuously for T1DM individuals. It has been suggested for T2DM individuals that reversibility would be the preferable route of research and development.

The bionic pancreas system developed at Boston University proved better than either conventional or sensor-augmented insulin pump therapy at managing BG levels in patients with T1DM living at home, with no restrictions, over 11 days (El-Khatib et al., 2017).

1.19 Carb matching

Carb matching is where the amount of insulin given is matched to the amount of carbohydrates eaten at mealtimes. This involves reading labels and weighing food portions until it becomes second nature. Carb matching has become popular as a planned diet is not required unlike the using method of fixed insulin injections. This method of treatment is mainly aimed at T1DM but if calories are controlled a similar idea could be used for insulin dependent T2DM people.

1.20 Acute Problems

1.20.1 Hyperglycaemia

Hyperglycaemia is the major symptom of T2DM and T1DM and occurs where BG concentrations are above normoglycaemia where BG levels are between 4 to 8 mmol/L (Wile and Wilding, 2014). Hyperglycaemia is where BG levels are between above 7 mmol/L when fasting and 11 mmol/L 2 hours after meals (Diabetes.co.uk, 2019).Hyperglycaemia can cause diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS). Many T2DM are not aware they are having a hyperglycaemic episode as symptoms may not develop until BG concentrations exceed 12 mmol/L. BG concentrations exceeding 7 mmol/L for extended periods of time can start to cause damage to organs and increase risk of CVD and reducing life expectancy (Pistrosch, Natali and Hanefeld, 2011).

1.20.2 Hypoglycaemia

Hypoglycaemia occurs when BG levels drop below normoglycaemia. The defined BG level of a hypo is below 4.0 mmol/L (NHS, 2017). A hypo is commonly a problem in T2DM and T1DM individuals using insulin treatment where there is too much insulin relative to food intake which is a problem of insulin injection methods rather than diabetes itself. This can also occur with sulphonylureas and meglitinides. The main symptoms of hypoglycaemia are sweating, fatigue and feeling dizzy but they can also include weakness, confusion and a raised heart rate, being pale, feeling hungry and blurred vision. Some T1DM individuals suffer with hypo unawareness where they do not notice the symptoms of a hypo until they go into a severe hypo which can include convulsions, unconsciousness and in rare cases a coma.

1.20.3 Diabetic ketoacidosis

DKA is the reduced blood pH associated the high concentration of ketones present with insulin deficiency, hyperglycaemia and dehydration. DKA usually occurs in T1DM and commonly during the development of diabetes, missed injections or malfunctioning insulin pumps. Without insulin not only will glycogen not be formed to reduce BG but no energy is available from glycolysis. The body will then seek out alternate sources to break down into fuel. When the body breaks down fat it leaves ketones in the blood stream that are acidic together with high blood sugar when these build up the body goes into a state of DKA. They body will show many warnings or symptoms such as frequent urination, thirst, heavier breathing, tiredness and distinctive smelling breath like nail varnish or fruit.

1.20.4 Hyperosmolar hyperglycaemic state

HHS is a potentially life-threatening complication that is a result of prolonged hyperglycaemia. HHS usually occurs with T2DM patients with very high BG levels and can develop through dehydration combined with illness. When excess BG levels are present the body will attempt to reduce these levels by urination causing dehydration. HHS does not have presence of ketones like DKA because development of ketones occurs due to lack of insulin. T2DM patients still produce some insulin so ketones will not be created for DKA to occur.

1.20.5 Hypertension

Hypertension occurs when blood pressure is above 140/90 mmHg. Ideal blood pressure is between 90/60-120/80 mmHG (NHS, 2019b). Hypertension is associated with higher CVD risk. T2DM have higher prevalence of hypertension and combined with obesity increases prevalence (Anari et al., 2017). Obesity is associated with diastolic dysfunction. Dysfunctional cardiac responses in people with obesity are reversible after weight loss.

1.21 Chronic problems

Chronic hyperglycaemia is central to the pathophysiology of chronic complications such as cardiovascular and peripheral vascular disease, retinopathy, nephropathy, and neuropath. It glycosylates not only haemoglobin to form HbA1c readings but also many other proteins including vital structural and functional types such as enzymes and kidney structure.

1.21.1 Obesity

Obesity is a medical condition where excess body fat is accumulated to a point where there is a negative effect on health. Body mass index (BMI) is an obesity indicator calculated by dividing an adult's weight and height in metres squared. T2DM people have increased BMI. A BMI of 18.5-24.9 kg/m^2 indicates a normal weight whilst a BMI between 25-29.9 kg/m^2 is classified as overweight. Obesity is defined as a BMI of 30-39.9 kg/m^2 (NHS, 2019c; Shields, 2006). It has been debated that the BMI results can be inaccurate as it does not take into account muscle mass, body fat or bone density (Shah and Braverman, 2012; Gallagher et al., 1996). BMI has strong intergenerational correlation between parent-child pairs but not for adoptee pairs which shows that there is a genetic correlation between BMI scores (Classen and Thompson, 2016). Obesity has a higher prevalence in more economically developed countries where excess food intake and sedentary lifestyles are more common. Obesity is a key symptom in metabolic syndrome.

Visceral fat accumulation in obesity does not just surround the abdominal area but is also in the organs and stop them function properly which was spoken about earlier. Obese subjects with visceral fat accumulation more frequently demonstrate impairment of glucose and lipid metabolism than those with subcutaneous fat accumulation. even in non-obese subjects visceral fat accumulation is correlated with glucose intolerance, hyperlipidaemia and hypertension (Matsuzawa et al., 1995). In a study performed by Steven et al. showed that a very low-calorie diet caused weight to fall from 98-83.8 kg and remained stable over 6 months (Steven et al., 2016).

1.21.2 Cardiovascular disease (CVD)

The deranged blood chemistry in diabetes raises the risks of atherosclerosis disease in blood vessels, heart and raises blood pressure to unsafe levels. Therefore T2DM have a 2-3 fold higher risk of CVD (Almdal et al., 2004) and nearly all patients in vascular ward suffer from DM (Cannell, 2016) and nerve damage compromise blood flow to toes, feet and lower limbs. Cardiovascular disease and heart failure are major causes of morbidity and mortality in people with T2DM (Juurlink et al., 2009). Diabetes, by driving inflammation and slowing blood flow, dramatically accelerates atherosclerosis where cytokines such as IL-6, IL-17a and TNFα are responsible for triggering the inflammatory cascade, all these stimuli promote abnormal attachment of leucocytes, such as monocytes and T-lymphocytes to the endothelial cells that lie in the artery lumen. Once inside the artery wall, monocytes differentiate into macrophages secreting IL-6 and TNFα. These macrophages progress to form lipid rich foam cells. IL-17a is produced by T-cells and aids in the recruitment of monocytes to the inflammation site continuing the process of inflammation and plaque build-up, as plaque builds up over time it can become unstable and vulnerable to rupture if the wall of the artery surrounding the plaque becomes weak and ruptures blood clotting components interacts with the substances of the plaque triggering a clot which may block the entire artery and causing a Heart Attack which may be fatal. This process however can be prevented.

1.21.3 Diabetic Neuropathy

Neuropathy is the disease or dysfunction of one or more peripheral nerves, typically causing numbness or weakness. Some people with nerve damage are without symptoms whilst other may have symptoms such as pain, tingling, numbness and loss of feeling in the hands, arms, feet and legs. If BG control and maintenance of feet is poor, neuropathy, poor blood supply and damage that results from neglect of skin pressure from shoes and other causes, may allow gangrene to develop and amputation may be needed to prevent systemic infection. There were 26378 lower limb amputations related to diabetes in England from 2014-2017, an increase of 19.4% from 2010-2013. Diabetes is the most common cause of lower limb amputation in the UK (Diabetes UK, 2018a).

1.21.4 Retinopathy

Retinopathy is the disease of the retina which results in impairment or loss of vision. T2DM Is the most common cause of vision loss and blindness in people of working age (BBC, 2016).

1.21.5 Diabetic nephropathy

Diabetic nephropathy or diabetic kidney disease is the chronic loss function in the kidney in those with T2DM. The mean treatment for diabetic nephropathy is ACE inhibitor medications which slows the progression of the disease by reducing proteinuria levels (Lim, A. K., 2014).

1.22 Oxidative stress

Diabetes is an inflammatory disease and one of the best ways to combat inflammation is to reduce oxidative stress. Oxidative stress reflects an imbalance between the concentration of reactive oxygen species and a biological system's ability to clear them or to repair the resulting damage (or the system will collapse as with a fulcrum that is not balanced). This is the case in diabetes where the damage caused by glucose is essentially driven by an oxidation process and can be thought of as accelerated aging in either T2DM or T1DM where glycosylated proteins and other age products result (Monaco, Gingrich and Hawke, 2019; Palmer et al., 2015). Normally the oxidation and reduction cycles in cells are coupled so that electrons are passed through related reactions.

Diabetes is an oxidative stress disease and the electron transport may be defective and cause aerobic metabolism to be less effective, thus making anaerobic mechanisms more likely at moderate intensity than it might otherwise be.

1.23 The Three Energy Systems that make ATP

Adenosine Triphosphate (ATP) is required for any muscle contraction or force exertion and as the human body does not store a significant amount of it but need a continuous supply. There are both anaerobic and aerobic energy systems that synthesize ATP which are the

ATP-PC system, glycolytic system, oxidative system. These 3 energy systems ‘interplay’, are always active and work simultaneously to fuel the body during exercise with one predominant system depending on the intensity, duration and repetition of effort required. An example of the progression of the three energy systems when going all-out would be an all-out sprint (ATP-PC system) to a slower jog (glycolytic system) to an eventual walk (Oxidative system). Exercise duration and intensity will determine the predominant system and thus how long the activity can be performed at that level. However, other factors influence what substrate and system are being used such as the fuels that are available, the fitness level of the subject and nutritional status. These factors may change over time with fitness levels, so energy metabolism is very individualized and dynamic. ATP is hydrolysed causing the triple phosphate group to split apart and release energy which results in adenosine diphosphate (ADP)+Pi. ADP gets phosphorylated back to ATP to quickly replenish the supply.

1.23.1 Adenosine Triphosphate Phosphocreatine (ATP-PC) System

During high intensity efforts of less than 10 seconds or repeated high intensity efforts of short duration activity such as weightlifting the dominant energy system is the ATP-PC system. The ATP-PC system takes place within the sarcoplasm of the muscle and is fuelled by CP, which is in limited supply and is depleted quickly. When the CP is depleted, the glycolytic system will be dominant for high intensity activities until the muscles CP stores are replenished. The ATP-PC system functions without oxygen and is available to use at any time. When there is a sudden increase in energy demand such as sprinters, shot putters or weightlifting the ATP-PC system is used. During the first few seconds of any activity stored ATP supplies the energy for a few seconds after that PC cushions the decline of ATP. As the ATP-PC system relies on CP, when supplies diminish the body must call on another energy system such as the glycolytic or oxidative system to produce ATP. It is estimated that the ATP-PC system can create energy at approximately 36 calories per minute. The ATP-PC system is the most direct and quickest form of energy production but can only supply enough energy for a short burst intense activity like a maximum weight lift or a sprint. The ATP-PC system does not create energy for a long enough to create a great deal of waste products.

1.23.2 Glycolytic system

The glycolytic system is the dominant system during activities above 85% maximum effort and exceeding 10 consecutive seconds of high intensity efforts. Specifically, this applies when there has been insufficient time to recover PC stores since the last similar effort when the ATP-PC system cannot be dominant during ongoing high intensity efforts such as long sprints. It is estimated that glycolysis can create energy at approximately 16 calories per minute.

After the ATP-PC system has been fully utilised the glycolytic system is the next suitable energy system to take advantage of. The glycolytic system is fuelled by glucose that circulates in the blood or glycogen in the muscles and liver which are supplied from dietary carbohydrates. Like the ATP-PC system the glycolytic system does not require oxygen for the actual process and is therefore anaerobic.

The glycolytic system involves 'fast' and 'slow' glycolysis. After the ATP-PC system has been exhausted, after around 12 seconds, the following 30 seconds of activity results in lactic acid accumulation, a decrease in power and muscle fatigue. This is called 'fast' glycolysis which is more powerful than 'slow' glycolysis, but pyruvic acid is reversibly converted to lactic acid and fatigue happens.

Then further effort up to approximately 50 seconds results in another drop-in power with ‘slow glycolysis’. ‘Slow’ glycolysis has relatively less power, but pyruvic acid is converted to acetyl coenzyme A (acA) and fed through the Krebs cycle where more ATP is produced therefore fatigue becomes delayed. Therefore, fatigue can be avoided in slow glycolysis compared to fast glycolysis. The glycolytic system is sometimes known the lactate system as waste products such a lactic acid accumulate in the blood and muscle cells. Symptoms of lactic acid build up consist of a burning sensation in the muscle, shortness of breath and fatigue.

This mechanism contributes ATP fuel for 1 to 3 minutes of intense activity when oxygen is scarce. The breakdown creates ATP as glucose is converted into 2 molecules of pyruvate. Hydrogen produced during the process can combine with pyruvate and if oxygen is present, the aerobic system can use more ATP. Often the aerobic system may accumulate too much hydrogen so instead the hydrogen combines with the pyruvate to create lactic acid. Lactic acid then enters the blood stream and is cleared by the liver.

If lactate production exceeds lactate clearance i.e. the lactate or anaerobic threshold reached, the lactic acid begins to accumulate in the blood. The lower blood pH inhibits the use of fatty acids for energy production through anaerobic metabolism and therefore increases the body’s dependence on carbohydrate and glycolysis. Muscles begin to fatigue and performance is diminished as blood lactate levels continue to rise and carbohydrate stores become depleted

An anaerobic threshold depends on the fitness of the subject. Through adaptations made during proper endurance training an athlete can increase their lactate threshold. Those with a better health or fitness level have a higher lactate threshold level. Therefore Anaerobic or lactate threshold levels are an excellent indicator for predicting endurance capacity (Powers and Howley, 2007).

Delevatti's study indicated an agreement between the glycaemic and second ventilatory methods in determination of the anaerobic threshold of T2DM individuals there for either method can be used for these patients (Delevatti et al., 2018; Sales et al., 2011).

1.23.3 The Oxidative system

Initially maximum effort is fuelled by the ATP-PC system, then as performance declines continued effort results in further decline through 'fast' or 'slow' glycolysis. Then the low power but longer duration oxidative system becomes more dominant and is estimated to create approximately 10 calories per minute. The oxidative system relays on the availability of oxygen. The oxidative system is dominant during activity that is below 85% maximum effort or when heart rate is sufficient enough for the necessary oxygen delivery. This aerobic activity is predominantly used for low intensity exercises that last anywhere from two minutes to a few hours, activities such as long distant running, swimming, rowing but also resting, walking and sleeping.

The oxidative system is fuelled by glucose and ultimately glycogen, adipose and intramuscular fats and in extended activities. Also in rare cases, where carbohydrates are depleted and stored fat is minimal, protein can be used as a last resort for energy production. Amino acids can be either converted to glucose via gluconeogenesis or other sources used in the Krebs cycle such as acA. Fats have a large storage capacity and provides over twice as much energy per gram than protein or carbs, making it a very attractive and efficient choice for energy production.

As fatty acids take more time to break down than glucose, more oxygen is needed. If efforts are intense and the cardiovascular system cannot supply oxygen quickly enough, ATP must be produced from carbohydrates in the Krebs cycle but in very long duration activities such as marathons carbohydrates become depleted and unless supplement by energy drinks then the body switches to fat as the energy producer.

In the Oxidative system the ATP can be produced in three ways, the Krebs cycle, electron transport chain and beta oxidation of fats. The Krebs cycle is a sequence of chemical reactions that continue to oxidize the glucose that was initiated during glycolysis. The acA enters the Krebs cycle and is broken down into carbon dioxide and hydrogen then two more ATP molecules are formed. The hydrogen produced in the Krebs cycle and during glycolysis causes the muscle to become too acidic if not dealt with, so the hydrogen combines with the cofactors NAD and FAD and is sent to the electron transport chain. Through more chemical reactions in the electron transport chain, hydrogen combines with oxygen, energy is produced, and acidity is prevented. This takes time as this process needs oxygen and is the reason that intensity of effort declines.

The Krebs cycle and electron transport chain metabolizes triglycerides and carbohydrates to produce ATP. The breakdown of triglycerides which is called lipolysis creates by-products called glycerol and free fatty acids. However, before free fatty acids can enter the Krebs cycle and enter the process of beta oxidation where a series of chemical reactions downgrades them to acA and hydrogen. The acA enters the Krebs cycle and fat is metabolized just like carbohydrates. The oxidative system provides energy much more slowly than the anaerobic energy systems but has generous supply and is much more efficient.

It is estimated that the ATP-PC and glycolytic systems can be improved up to 20% and the oxidative system by 50% when training sedentary subjects. But genetically determined muscle fibre composition plays a huge role. The muscle contains either predominantly slow type 1 fibres which are more efficient in endurance activities or fast type 2 fibres which are more suitable for strength activities.

In prolonged activities where intensity is low the body will use fat as a main energy source and spare the use of muscle glycogen and BG so that it is available for use if exercise intensity increases and oxygen availability is decreased.

1.24 Anaerobic and aerobic exercise

Anaerobic metabolism is not a pathway that functions in the absence of oxygen but rather does not use oxygen. In sports that require repeated short bursts of exercise, for example sprinting or weightlifting, the anaerobic system enables muscles to recover for the next burst. Anaerobic or lactate threshold (AT) is a predictor of endurance performance. This is the point in which progressive increases in blood lactate occur.

The classic way of assessing the AT referred to earlier is to assess blood lactate throughout the exercise session and identify the point that blood lactate starts to accumulate although it is not always convenient to take samples through the test.

Individuals with a naturally high oxygen uptake should complement this with a rigorous training programme in order to achieve maximal performance. However, any individual such as untrained people or T2DM people can still improve their anaerobic performance by doing this (Ghosh, 2004).

Aerobic exercise includes lower intensity activities performed for longer periods of time and relates to lactate levels above the AT. For a highly trained runner AT is typically 75 to 90% of V02 max and this means that their high energy (high ATP expenditure) is occurring at a higher fraction of their maximum O_2 uptake (%VO_2 max). For an average untrained person with diabetes it would be expected that the AT would occur below that of an average healthy untrained person with an AT of 50-60% of VO_2 max. Komatsu mentions that diabetic athletes have a lower AT (Komatsu et al., 2010)

1.25 How to measure anaerobic and aerobic exercise

The increased amount of technology over the last 50 years has made it easier to measure whether an exercise is aerobic or anaerobic. Exercise physiology has evolved during the last decade from using Douglas bags in the laboratory to using portable gas analysers to assess cardiorespiratory responses to exercise. There are more invasive methods such as muscle biopsies, which allow the researcher to determine the kinetics of aerobic or anaerobic metabolism during exercise (Bangsbo et al., 1996; Bangsbo et al., 1990).

1.26 Respiratory Exchange Ratio (RER)

The respiratory exchange ratio (RER) is the ratio between the amount of O_2 consumed and CO_2 produced in one breath. Humans typically inhale more O_2 than they exhale of CO_2. The RER can be used to estimate the respiratory quotient which indicates the fuel being used, fat or carbohydrate. When using RER in this way the subject should either be at rest or exercising mildly. RER should be about 0.8 at rest with a normal healthy diet. An RER of 0.7 indicates that fat is the predominant fuel source under these conditions and an RER of 0.85 suggests a mix of fat and carbs and a value of 1 or above indicates that carbohydrates are predominant fuel source. The RER value exceeds 1 during intense exercise. This is due to CO_2 production becoming greater by working muscles and more of the inhaled O_2 gets used rather than being expelled using RER to calculate respiratory quotient during intense exercise is inaccurate because of the lactate compensation system. For technical reasons this was not included in the study.

1.27 Inflammatory Biomarkers

There are inflammatory markers that are effective in the study of exercise in healthy an T2DM people. These are discussed below and some of them, interleukin-6, leptin, resistin, tumour necrosis factor, c-reactive protein, cystatin C were used in the practical part of this project.

1.27.1 Interleukin-6 (IL-6)

Interleukins are a group of cytokines which play an essential role in the function of the immune system. Cytokines are a large group of signalling proteins, peptides or glycoproteins that are secreted by cells of the immune system. Cytokines regulate a wide range of biological functions such as inflammation, repair and haematopoiesis. Interleukins primary function is to modulate growth and activation during inflammation and immune responses. IL-6 is an interleukin that acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine. A myokine is one of the many cytokines that are produced and secreted by muscle cells in response to muscular contractions. Il-6 elevates in response to muscle contraction and has various anti-inflammatory functions in its role as a myokine. IL-6 stimulates inflammatory and auto-immune processes in many diseases such as diabetes. Il-6 is secreted by produced and secreted by T and B lymphocytes, fibro blasts and macrophages. IL-6 influences the glucose metabolism it also increases the release of leptin. The anti-inflammatory effects of IL-6 cause the inhibition of TNFα from effecting the insulin signalling pathway to be inhibited. Contracting muscles contributes to most of the IL-6 present in circulation in response to exercise, this is to help with metabolism (Fischer, 2006). This is important for the inflammatory effects of visceral fat in diabetes and measurement of IL-6 is an important metric for looking at the effect of exercise on this condition, with the proviso that exercise itself is temporarily inflammatory. For the following measurements these cytokines may give important information about the effect of exercise on T2DM.

1.27.2 Leptin

Leptin is a hormone predominantly produced by adipose cells. Leptin helps to regulate energy balance by inhibiting hunger, which should diminish fat storage in adipocytes. Regulation of fat stores is the primary function of leptin. In obesity a decreased sensitivity to leptin occurs which results in an inability to feel full despite high energy stores and high levels of leptin. Leptin and adiponectin perform complimentary actions and can have shared effects. Adiponectin in combination with leptin has been shown to completely reverse insulin resistance in mice but only partially by either adiponectin or leptin alone (Yamauchi et al., 2001).

1.27.3 Resistin

Resistin is an adipocyte-derived polypeptide which was discovered in 2001 and has been found to cause high levels of low-density lipoprotein which increases the risk of CVD. Resistin increases the production of LDL in human liver cells and degrades LDL receptors found in the liver. Therefore, the liver is less able to clear LDL cholesterol from the body, which is considered “bad” cholesterol.

In Cobbold evidence suggests that resistin may be elevated in T2DM individuals and may also contribute to the impaired glucose tolerance and insulin resistance observed in T2DM. Cobbold hypothesized that resistin levels may drop in individuals following a long term aerobic and/or resistance exercise intervention programme (Cobbold, 2019).

1.27.4 Tumour necrosis factor α (TNFα)

TNFα is a cell signalling cytokine which is a member of the TNF superfamily. The primary role of TNFα is regulation of immune cells and the induction of fever and inflammation. TNFα prevents the phosphorylation of IRS1 and the PI3K pathway which causes the translocation of the GLUT4 carrier protein which allows glucose into the cell. In a study performed by Swaroop TNFα levels and BMI revealed a significant correlation. A significant correlation was also found between per cent beta cell function and TNFα (Swaroop, Rajarajeswari and Naidu, 2012).

1.27.5 C-reactive Protein (CRP)

CRP is synthesised by the liver in response to factors released by macrophages and fat cells. It is an acute phase protein which increases following IL-6 secretion. A high level of CRP in the blood is a marker of inflammation and can indicate inflammation in the arteries of the heart which leads to a higher risk of heart attack. CRP is frequently used in cardiovascular disease risk assessment. In a study performed by Fedewa at al. results suggested that engaging in exercise training is associated with a decrease in CRP levels and greater improvements in CRP level occur with a decrease in BMI (Fedewa, Hathaway and Ward-Ritacco, 2017).

1.27.6 Cystatin C

Cystatin C is a protein that is filtered out of the blood by the kidneys and mainly used as a biomarker of kidney function. Cystatin C is produced steadily by all nucleated cells in the body and is found in most tissues and body fluids. It has recently been studied for its role in predicting CVD. A study by Sahakayan et al. found that a positive relationship of serum cystatin C levels with the incidence of T2DM independently of cofounding risk factors (Sahakyan et al., 2011).

1.28 Research questions

The research questions seeking to be answered for this study are as follows.

1, How does a structured exercise programme affect T2DM volunteers compared to non-diabetic volunteers?

2, How do different types of structured exercise programmes affect T2DM volunteers compared to non-diabetic volunteers?

3, How inflammatory markers are affected by a structured exercise programme involving a combination of cardio and resistance exercise in T2DM volunteers compared to non-diabetic volunteers?

Chapter 2 Materials and Methods

2.1 Introduction

This chapter will describe the methods and materials used to collect the data for this study. Each volunteer that participated in the study completed a structured exercise programme lasting 6 weeks involving 12 exercises sessions of either cardio exercise, resistance exercise and a combination of both. The resistance exercise was performed on a "Bodycraft Jones" Smith machine displayed in Figure 5. The cardio exercise of cycling was performed using a "Corival recumbent" ergometer bicycle manufactured by Lode displayed in Figure 6. Three OGTTs where completed at different points in the study, one week prior to the 1st exercise session, the day following the 1st exercise session and the day following the 12th exercise session.

Figure 5, displays a photo showing the "Bodycraft jones" smith machine.

Figure 6, displays a photo showing the "Lode corival recumbent" bicycle.

2.2 Recruited volunteer sample

Table 1, Showing group sample size and gender

Exercise Programme Group	n=20	Male=12	Female=8
T2 Combination	n=5	M=2	F=3
T2 Cardio	n=3	M=2	F=1
T2 Resistance	n=3	M=3	F=0
ND Combination	n=5	M=3	F=2
ND Cardio	n=2	M=0	F=2
ND Resistance	n=2	M=2	F=0

Sample size would preferably have been larger but due to time, lab and financial restrictions this was not possible. Volunteers completed their preferred exercise programme.

2.3 Structured exercise programme

Table 2, Structured exercise programme timetable

Week	Session
Week 1	OGTT Session 1
Week 1	One Repetition Maximum Session 1
Week 2	Exercise Session 1
Week 2	OGTT Session 2
Week 2	Exercise Session 2
Week 3	Exercise Session 3
Week 3	Exercise Session 4
Week 4	Exercise Session 5
Week 4	Exercise Session 6
Week 4/5	One Repetition Maximum Session 2
Week 5	Exercise Session 7
Week 5	Exercise Session 8
Week 6	Exercise Session 9
Week 6	Exercise Session 10
Week 7	Exercise Session 11
Week 7	Exercise Session 12
Week 7	OGTT Session 3
Week 8	One Repetition Maximum Session 3

Each programme consisted of 12 exercises sessions, 3 OGTT sessions and three one repetition maximum sessions. The 12 exercises sessions were the only factors that separated each exercise programme. The exercise sessions occur twice a week at a suitable and convenient time for the volunteer around their working life. The three OGTT sessions take place one week prior to the volunteers first exercise session, the day following the 1^{st} exercise session and the day following the 12^{th} exercise session. The 1RM sessions take place in week 1, one week prior to the 1^{st} OGTT, the second 1RM will take place after the 6^{th} exercise session and the 3^{rd} 1RM will take place after the 3^{rd} OGTT session. The OGTT sessions were structured to specifically collect data before the volunteer started the structured exercise programme, after the 1st exercise session and after the 12^{th} exercise session for baseline, acute and chronic changes.

2.3.1 Combined cardio and resistance exercise programme sessions

Table 3, Combination programme exercise session plan

Combination Programme
Warm up
Resistance Set 1 – 5 x 10
Rest time
Resistance Set 2 – 5 x 10
Rest time
Resistance Set 3 – 5 x 10
Rest time
Cycling – 20 minutes
Cool down

When the volunteers arrived for the exercise session they were asked to wear the T34 polar heart rate monitor and sit down for at least 10 minutes before blood pressure, heart rate and BG levels were measured to enable accurate starting baseline measurements. The volunteer was then asked to warm up by performing 17 allocated stretches and five minutes cycling.

When the volunteers were warmed up and were ready to exercise they were asked to start the first set of resistance exercise consisting of 10 repetitions of five different exercises. The five exercises include barbell squat on a smith machine, incline chest barbell press on the smith machine, lateral back pull down using a cable, tricep pull down using a cable and bicep curl using a cable. This was then repeated over 3 sets. The volunteer performed these exercises at 50-60% intensity of their maximum strength determined from the one-repetition maximum test. Immediately after each set of resistance exercise RPE, heart rate and BG were measured in the five minutes of rest time.

After the final set of resistance exercise RPE, heart rate, BG and blood pressure were measured again. Immediately after these halfway tests the volunteer was asked to sit on the recumbent bicycle whilst the respiratory mask is attached. The volunteer was then asked to start cycling and reach their target heart rate zone and keep within it. Once their heart rate was between 50 to 60% intensity the 20 minutes begins. At 10 minutes of cycling RPE, BG and heart rate are measured. At the end of the 20 minutes cycling RPE, BG, heart rate and blood pressure are measured before the volunteer was asked to cool down by performing the 17 allocated stretches.

2.3.2 Cardio exercise programme sessions

Table 4, Cardio programme exercise session plan

Cardio Programme
Warm up
Cycling – 20 minutes
Rest time
Cycling – 20 minutes
Rest time
Cool Down

When the volunteers arrived for the exercise session they were asked to wear the T34 polar heart rate monitor and sit down for at least 10 minutes before blood pressure, heart rate and BG levels were measured to enable accurate starting baseline measurements. The volunteer is then asked to warm up by performing 17 allocated stretches and five minutes cycling.

When the volunteers were warmed up and ready to exercise they were asked to sit on the recumbent bicycle whilst the respiratory mask was attached. The volunteer was then asked to start cycling and reach their target heart rate zone and keep within it. Once their heart rate is between 50 to 60% intensity the 20 minutes begins. At 10 minutes of cycling RPE, BG and heart rate were measured. At the end of the 20 minutes cycling RPE, BG, heart rate and blood pressure are measured. The mask was then taken off and the volunteer was asked to rest for 10 minutes. At the end of the 10 minutes break heart rate and BG was measured before getting back onto the recumbent bicycle. Once the mask is put back on the volunteer was asked to reach their target heart rate zone and keep within it once more. At 10 minutes of cycling RPE, BG and heart rate were measured. At the end of the 20 minutes cycling RPE, BG, heart rate and blood pressure were measured then the volunteer is asked to cool down by performing the 17 allocated stretches.

2.3.3 Resistance exercise programme sessions

Table 5, Resistance programme exercise session plan

Resistance Programme
Warm up
Resistance Set 1 - 8 x 10
Rest time
Resistance Set 2 – 8 x 10
Rest time
Resistance Set 3 – 8 x 10
Cool down

When the volunteers arrived for the exercise session they were asked to wear the T34 polar heart rate monitor and sit down for at least 10 minutes before blood pressure, heart rate and BG levels were measured to enable accurate starting baseline measurements. The volunteer was then asked to warm up by performing 17 allocated stretches and five minutes cycling.

When the volunteers were warmed up and ready to exercise they were asked to start the 1st of 3 sets of resistance exercise consisting of 10 repetitions of 8 different exercises. The 8 exercises consisted of Barbell squat on a smith machine, shoulder barbell press on smith machine, incline chest barbell press on a smith machine, flat chest barbell press on a smith machine, lateral pull down using a cable, tricep pull down using a cable, bicep curls using a cable, and upright row using a cable. Immediately after the 1st set of exercise RPE, heart rate and BG were tested. The volunteer then performed the 2nd set of resistance exercise. Immediately after the 2nd set of exercise RPE, heart rate, BG and blood pressure were taken. The volunteer was then asked to perform the 3rd set of resistance exercise. Immediately after the 3rd set of resistance RPE, BG and heart rate are taken. The volunteer was then asked to perform the 17 allocated stretches to cool down. Blood pressure, BG and heart rate were then taken.

2.4 Oral glucose tolerance test session (OGTT)

3 Oral glucose tolerance tests were performed on each volunteer. The 1st OGTTs were carried out 1 week prior to the volunteers 1st exercise session. The 2nd OGTT took place the day after the 1st exercise session. The 3rd OGTT took place the day after the 12th exercise session which are baseline, acute and chronic data points in the study.

The OGTT sessions lasted between 2:30-3 hours. The volunteer was asked to arrive at the exercise physiology laboratory in a fasted state of 10-12 hours. The basal metabolic rate was measured for 20 mins through the gas analyser whilst the volunteer is in the fasted state.

The 1st blood sample is taken at time=0 then taken and the volunteer is asked to consume 75 g of dextrose with 300 ml of water. 13 BG tests were taken every 10 minutes from 0 – 120 minutes. 4 venepuncture blood samples were taken at 0, 30, 60 and 120 minutes for use with the Randox Investigator.

Fasting blood glucose, Post-prandial blood glucose, OGTT time to peak, OGTT peak and OGTT area under curve were all measured during the OGTT. Additionally, BMR, HbA1c, Lipid profiles, weight, height, waist, BMI, lung capacity, resting heart rate and blood pressure were taken at this session for baseline, acute and chronic data points.

2.5 One-repetition maximum sessions

The one-repetition maximum (1RM) test was used to determine the same relative weight to be lifted by each volunteer in the exercise sessions. In the resistance exercise sessions 50-

60% of each volunteers 1RM was used for each exercise. 50-60% was chosen to represent moderate exercise for health and safety reasons and to guarantee ethical approval.

The 1RM test was carried out before the first exercise session, after the 6th exercise session and after the 12th exercise session. The volunteer's maximum strength was determined by asking them to 'max out' to failure on each exercise between 1-6 reps. The Brzycki equation (1RM = 100 x weight / (102.78 - 2.78 x repetitions)) was used to determine the volunteers maximum one-repetition lift weight (Brzycki, 2000).

2.6 Target heart rate zone for cycling

Each volunteer were asked to cycle in a target heart rate training zone determined from the Karvonen formula (Target heart rate = ((maximum heart rate – resting heart rate) x %intensity) + resting heart rate) (Karvonen, Kentala and Mustala, 1957). The formula uses maximum and resting heart rate with the required training intensity to get a target heart rate. The resting heart rate is taken during the OGTT session. The volunteer is asked to cycle within the target heart rate training zone of 50-60% intensity which represents a suitable moderate exercise for the volunteers due to health and safety reasons and to guarantee ethical approval.

2.7 Fasting blood glucose

Fasting blood glucose levels were taken during the oral glucose tolerance test. The first BG sample at 0 was taken at a fasted state of 10-12 hours. This reading was taken at all 3 OGTT's.

2.8 Blood glucose

BG tests were taken during the OGTT session and each exercise session. Each BG test starts by wiping the allocated finger with an alcohol wipe. Once the finger was dry a Bayer Microlet lancet was used to pierce the fingertip and the first drop of blood was wiped away. The second drop of blood was measured by a Bayer contour BG monitor.

2.9 Blood pressure

All blood pressure measurements were taken using an Omron M3 blood pressure monitor. The blood pressure cuff was placed on the upper arm and was measured whilst the volunteer has been sat at rest for at least 5 minutes. Blood pressure was taken at points in the exercise sessions and in the OGTT sessions for baseline, acute and chronic results.

2.10 Heart rate

A T34 polar chest strap monitor was used to measure heart rate. Whilst the volunteer was performing resistance exercise the chest monitor was connected to a FT1 watch. Whilst the volunteer is cycling the chest monitor was connected to the ADInstruments Lab Chart programme.

2.11 HbA1c tests

HbA1c was measured using a Quo test EKF diagnostics HbA1c analyser. A Bayer Microlet lancet was used to pierce the fingertip of the volunteer where a large drop of blood was collected on the finger and is collected and placed into the analyser using the supplied tool.

The results are ready within 5 minutes. A Hba1c test was given to the volunteers on the OGTT Baseline and chronic sessions.

2.12 Cholesterol tests

Cholesterol was measured using a Cholestech LDX lipid profiler. A 5 ul blood droplet is pipetted into the lipid profile cassette and analysed by the profiler. The profiler gave the results for total cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL), non-HDL and triglycerides. A cholesterol test was given to the volunteers on the OGTT Baseline and chronic sessions.

2.13 Resting heart rate

Resting heart rate was measured at the lowest point whilst the volunteer is at rest for 20 minutes. A T34 polar chest strap monitor was used to measure heart rate. This was taken during the OGTT sessions.

2.14 Body measurements

Weight was measured with no footwear in KG using a Seca automated scales SN:808251073074. Height was measured with no footwear in CM using a Seca stadiometer. BMI was determined by using weight and height (BMI = weight (KG) / Height^2 (M)). Waist was measured using a measuring tape in CM. These measurements were taken during the baseline and chronic OGTT sessions.

2.15 Peak expiratory flow test

Peak expiratory flow is a measurement of how quickly a patient can blow air out of the lungs. The Peak expiratory flow rate (PEFR) was taken at the start and the end of the exercise programme. PEFR was recorded using a peak flow meter. The volunteer was asked to take a deep breath and exhale as hard as they can through the peak flow meter. This was taken during the baseline and chronic OGTT sessions.

2.16 Borg rating of perceived exertion

The Borg rating of perceived exertion was used to determine how intense the exercise felt to the volunteer. The volunteer was asked how much effort they exerted after every set of resistance exercise and after every 10 minutes of cardio exercise.

2.17 Resting metabolic rate

Resting metabolic rate was determined by using an AD instruments gas analyser. During the baseline and post intervention OGTT sessions volunteers were asked to arrive at the exercise physiology laboratory at a fasted state of 10 to 12 hours. The volunteer was asked to be seated in a reclined position for 30 minutes. The volunteer was asked to wear a mask with a nose clip. The volunteer's respiration was recorded for the duration of the test to determine VO_2 and CO_2 levels for the Weir equation. The Weir equation was used to determine the volunteers RMR (kCal = [(3.941 x VO2) + (1.106 x VCO2)] x 1.44) (Weir, 1949).

2.18 Randox Investigator

The Randox Investigator is a machine that carries out multiple Elisa tests that work using an antibody sandwich immune-luminescence assay. The Randox Investigator was used to detect quantify inflammatory markers from the blood samples using Metabolic Syndrome Array I and II.

*Table 6, Shows metabolic syndrome arrays I and II. * did not test*

Metabolic syndrome array I	**Metabolic syndrome array II**
Ferritin*	Adiponectin*
Interleukin-6 (IL-6)	C-reactive Protein (CRP)
Insulin*	Cystatin C
Leptin	
Plasminogen Activator Inhibitor-1 (PAI-1)*	
Resistin	
Tumour Necrosis Factor α (TNFα)	

2.19 Insulin sensitivity

Insulin sensitivity was determined by using the blood samples taken during the OGTT. Insulin sensitivity was measured using the Matsuda index (10,000/square root of [fasting glucose x fasting insulin] x [mean glucose x mean insulin during OGTT]) which uses plasma glucose and insulin levels to determine insulin sensitivity in T2DM subjects (Matsuda and DeFronzo, 1999).

2.20 Venepuncture collection

All venous blood samples were collected using the BD Vacutainer system into 10 ml EDTA blood collection tubes. In the cubital fossa area, the median cubital vein was the preferred vein of collection although the cephalic and basilica vein were also used. The blood samples were centrifuged for 15 minutes at 4300 rpm at 4°C Using a ThermoFisher Scientific

Legend23R centrifuge to separate the erythrocytes and the blood plasma. The blood plasma was then transferred into 2ml Eppendorf tubes and stored at -80°c ready for analysis.

21 blood samples are collected over the 6 to 8 weeks. 12 samples were taken during the three OGTTs. Three samples were taken pre, during and post exercise during the first exercise session. 6 samples were taken post exercise on the 2nd, 4th, 6th, 8th. 10th and 12th sessions.

2.21 Researcher training

The researcher was required to be well prepared for any risks that might have occurred during the study therefore attended an advanced first aid at work and defibrillation course. The researcher was fully qualified in the BD vacutainer method of venepuncture. The researcher also took part in the ADInstruments training course.

2.22 Ethical approval

Ethical approval was approved by De Montfort University Leicester, School of Pharmacy, Faculty of Health and Life Sciences, Research Ethics Committee. All volunteers were required to provide full written informed consent (appendix 3 and 4). All volunteers were required to go through a health screening process involving filling out a health screen form. All volunteers were provided with volunteer information sheets (appendix 1 and 2) including details of the exercise programme and blood samples.

2.23 Recruitment of volunteers

The recruitment of volunteers involved an advert on the De Montfort University student and staff login home pages and posters on the walls (appendix 5) and notice boards around the university campus. There were adverts placed in the Leicester Mercury. There was also an email sent out to the DMU staff, alumni and past and present students. Posters were also distributed to the local pharmacies and De Montfort University Queen Elizabeth II Leisure Centre. There was also a stall at the De Montfort University Freshers' welcoming weekend.

The volunteers must go through a screening process to make sure they are suitable for the programme. They are asked to come into the exercise physiology laboratory for an introductory session where they will find out more about the exercises, equipment and tests. It is essential the volunteer has enough time and determination to commit to the exercise programme at least twice a week. Full medical history and any other health issues are checked to make sure it is safe for the volunteer to take part. Heart pains and joint pains may exclude people from taking part. All volunteer data is anonymised.

2.24 Incentive for volunteers

Each volunteer received a 50% subsidised membership at the De Montfort University's Queen Elizabeth II Leisure Centre at the end of the completed exercise programme. This was to reward the volunteers for their commitment to our programme but also encourages the volunteers to continue to integrate exercise as part of their weekly routine in order to maintain a healthy lifestyle. This incentive increased the interest in recruitment for our exercise programme. The volunteers also had the incentive of discovering information about their general health such as HbA1c level, cholesterol levels, BMR, insulin sensitivity, resting heart rate and fasting blood glucose.

2.25 Statistical Analysis

Statistical analysis was formulated within Microsoft Excel. Throughout the study data has been presented using mean and standard deviation. Baseline to post intervention results were assessed using paired t-tests which were considered significant with a p-value < 0.05.

Chapter 3 Results and Discussion

3.1 Introduction

This section shows the results of the study and the discussion. Here are results from all OGTT sessions which were taken from three points, Pre shows the baseline readings before the structured exercise programme started, post1 shows the acute results which were recorded after the 1st exercise session and post12 shows the chronic results which were recorded after all 12 exercise sessions were completed. The OGTT results include the OGTT curve, fasting blood glucose (FBG), post-prandial blood glucose (PPBG), OGTT peak blood glucose, OGTT time to peak and OGTT area under curve.

3.2 Oral Glucose Tolerance Test Results

3.2.1a Baseline OGTT Results

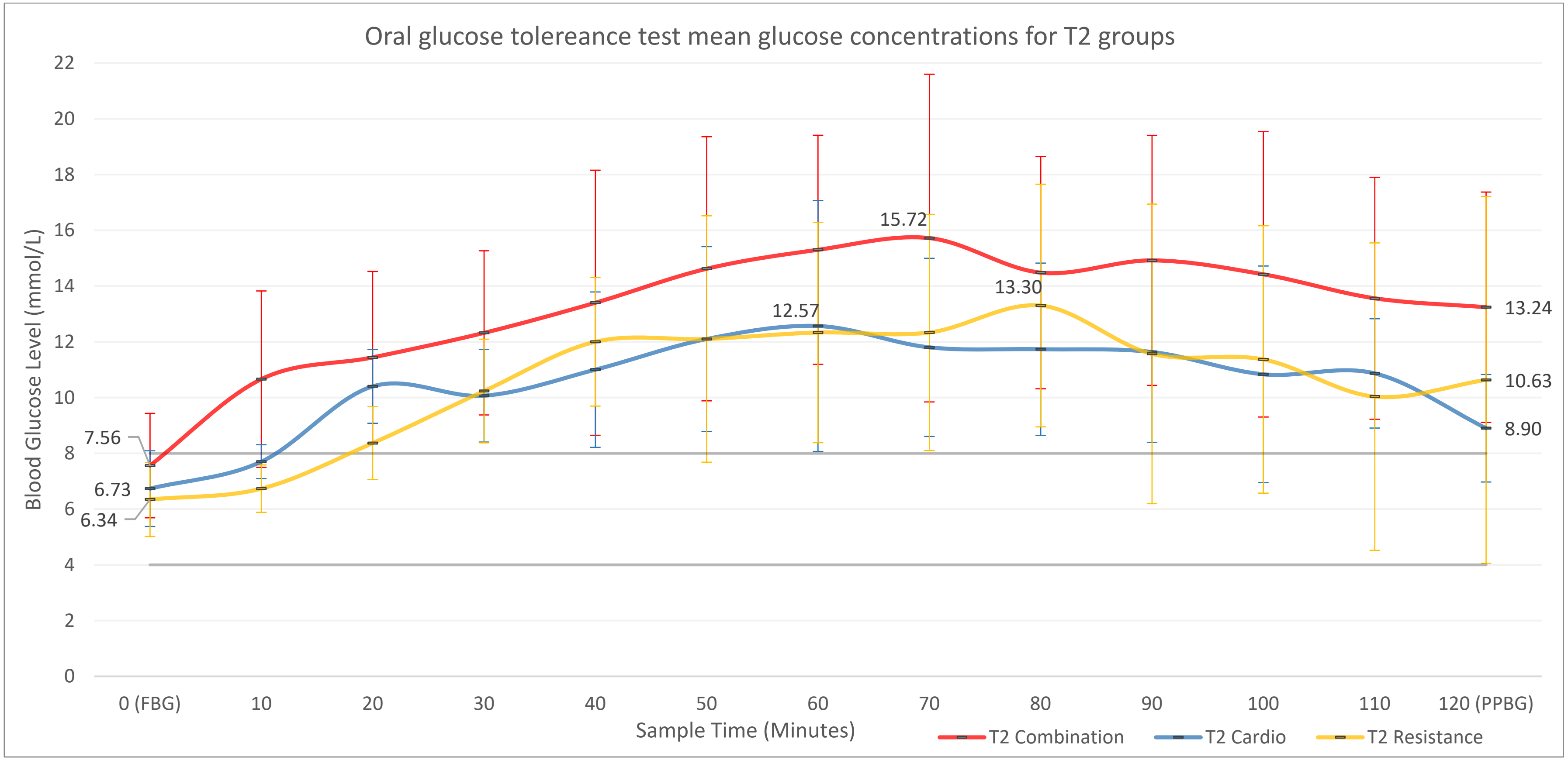

Figure 7, displays a line graph showing the three OGTTs mean and standard deviation results before the 1st exercise session for each T2 volunteer groups. Normoglycaemia range is shown in bold.

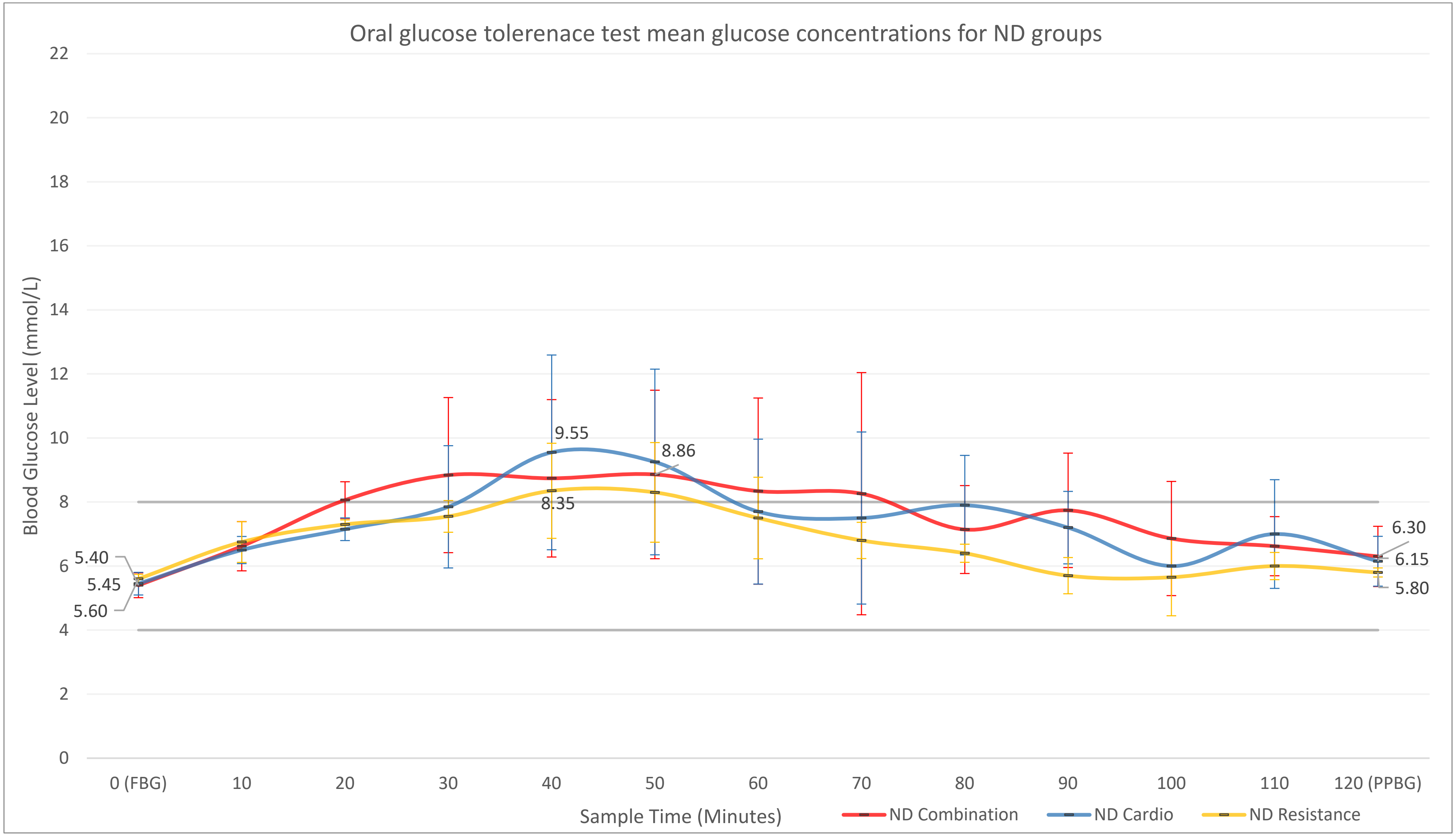

Figure 8, Displays a line graph showing the three OGTTs mean and standard deviation results before the 1st exercise session for each ND volunteer groups. Normoglycaemia range is shown in bold

The comparison of Figure 7 and Figure 8 for the T2 and ND groups baseline OGTT results are as follows.

- Figure 7 and Figure 8 shows the OGTT curve results of the volunteer groups at the starting baseline stage before any exercise sessions have taken place.
- Figure 7 shows that the T2 volunteers BG are well above the normal PPBG levels as expected i.e. above 8 mmol/L which is the defined level that a volunteer becomes classified as having diabetes mellitus.
- The volunteers were randomly allocated into sub-groups to ensure even baseline measurements however the post-prandial BG at the 120-minute mark for each T2 exercise group shows the PPBG levels to vary from 13.24, 10.63 and 8.90 mmol/L. The range would ideally by lower. In the future if the study were to be rerun it would be beneficial to group the T2 volunteers so that each group has a more similar mean PPBG starting level.
- In Figure 8 the ND volunteer groups are well within the normal range of 4 to 8 mmol/L as expected. Although BG levels did go slightly above the normal range between 20 to 80 minutes which may be due to the ND volunteers being recruited at a similar age and weight as the T2 volunteers. This may mean that the ND volunteers are at larger risk to T2DM than the average person.
- The ND OGTT results in Figure 8 at around 40 minutes indicates insulin has been released from the functioning pancreas in response to glucose entering the body as BG levels begin to decrease. The T2 OGTT results in Figure 7 show delayed pancreatic activity at 60 minutes. indicating a dysfunctional pancreas.
- However, the T2 graphs in Figure 7 show a steady increase of BG levels up until around 60 to 70 minutes. The T2 groups BG levels start to come back down at around 70 to 80 minutes but at a much slower rate than the ND groups which indicates a lack of pancreatic activity or impaired glucose tolerance.

- In Figure 8 the ND resistance group appears to have the most effective BG control at the start but still shows a good improvement compared to the post 12th exercise session of post-prandial BG levels shown in Figure 12.
- Figure 7 displays that the T2 control groups show a large standard deviation within their BG concentrations compared to Figure 8 with the ND control groups. The reason for this is that the ND control groups have a tighter level of BG control whilst the T2 control groups have impaired glucose tolerance therefore they will have a greater variance between each candidate.

3.2.1b OGTT results after the 1st exercise session

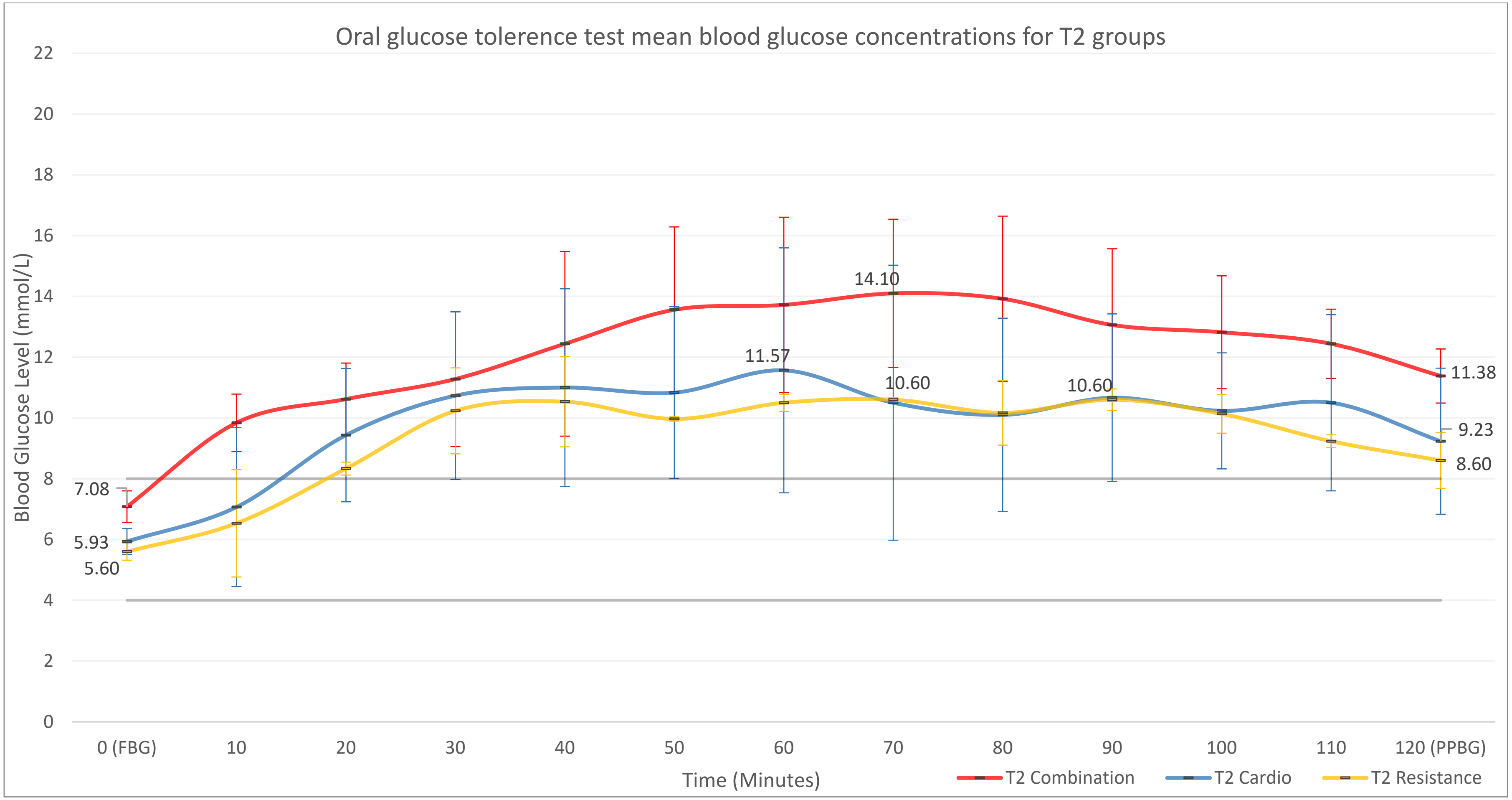

Figure 9, displays a line graph showing the three OGTTs mean and standard deviation results after the 1st exercise session for each T2 volunteer groups. Normoglycaemia range is shown in bold.

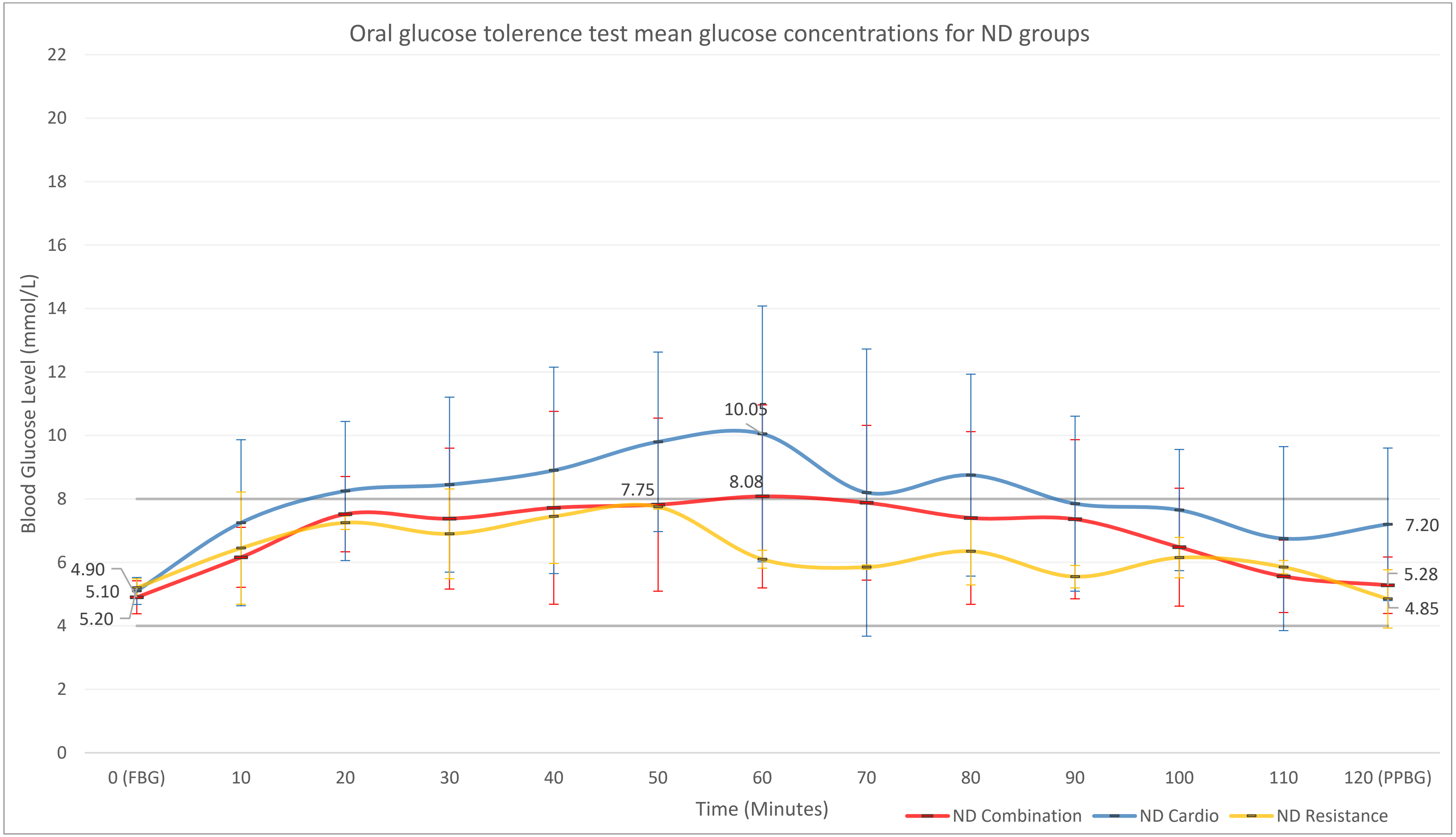

Figure 10, displays a line graph showing the three OGTTs mean and standard deviation results after the 1st exercise session for each ND volunteer groups. Normoglycaemia range is shown in bold.

The comparison of Figure 9 and Figure 10 for the T2 and ND groups OGTT results post 1st exercise session which shows the acute exercise changes are as follows.

- It appears that both PPBG levels at 120 minutes for T2 combination and resistance groups have reduced after 1 exercise session. In Figure 9 the T2 combination group has decreased from 13.24 mmol/L to 11.38 mmol/Ln whilst the T2 resistance group decreased from 10.63 mmol/L to 8.60 mmol/L.
- The same happened with the ND combination and resistance groups which shows a decrease in post prandial BG levels after 1 exercise session.
- Both T2 and ND cardio groups showed an increase in post prandial BG levels which may be due to the increased adrenaline as it is a stressful exercise. This stimulates the alpha cells to release glucagon which will cause the liver to release glucose from stored glycogen. This increases BG levels and causes a BG peak during cardio exercise.
- Comparing the post first session OGTT results with the pre first session it has been noticed that there is a larger improvement in post prandial BG for T2 combination and resistance groups than ND combination and resistance groups. It is expected that the T2 group would have more room for improvement in the results as they are generally unhealthier than the ND group.
- T2 combination group in Figure 9 shows a monophasic curve which may indicate improved glucose control after 1 exercise session. All the other curves of OGTT groups mean were biphasic, where a second increase in BG occurs after the initial peak.

3.2.1c OGTT results after the 12th exercise session

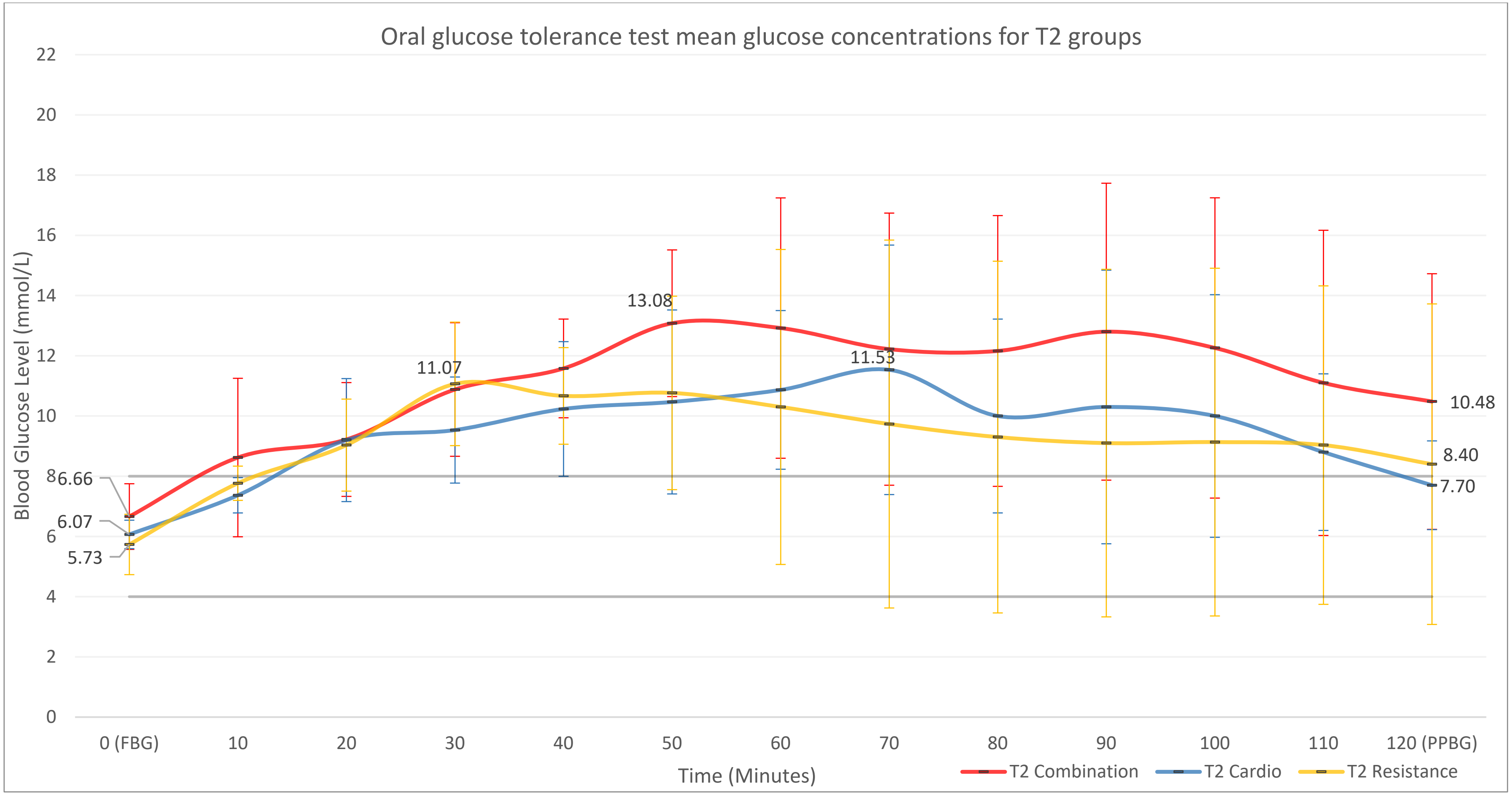

Figure 11, displays a line graph showing the three OGTTs mean and standard deviation results after the 12th exercise session for each T2 volunteer groups Normoglycaemia range is shown in bold..

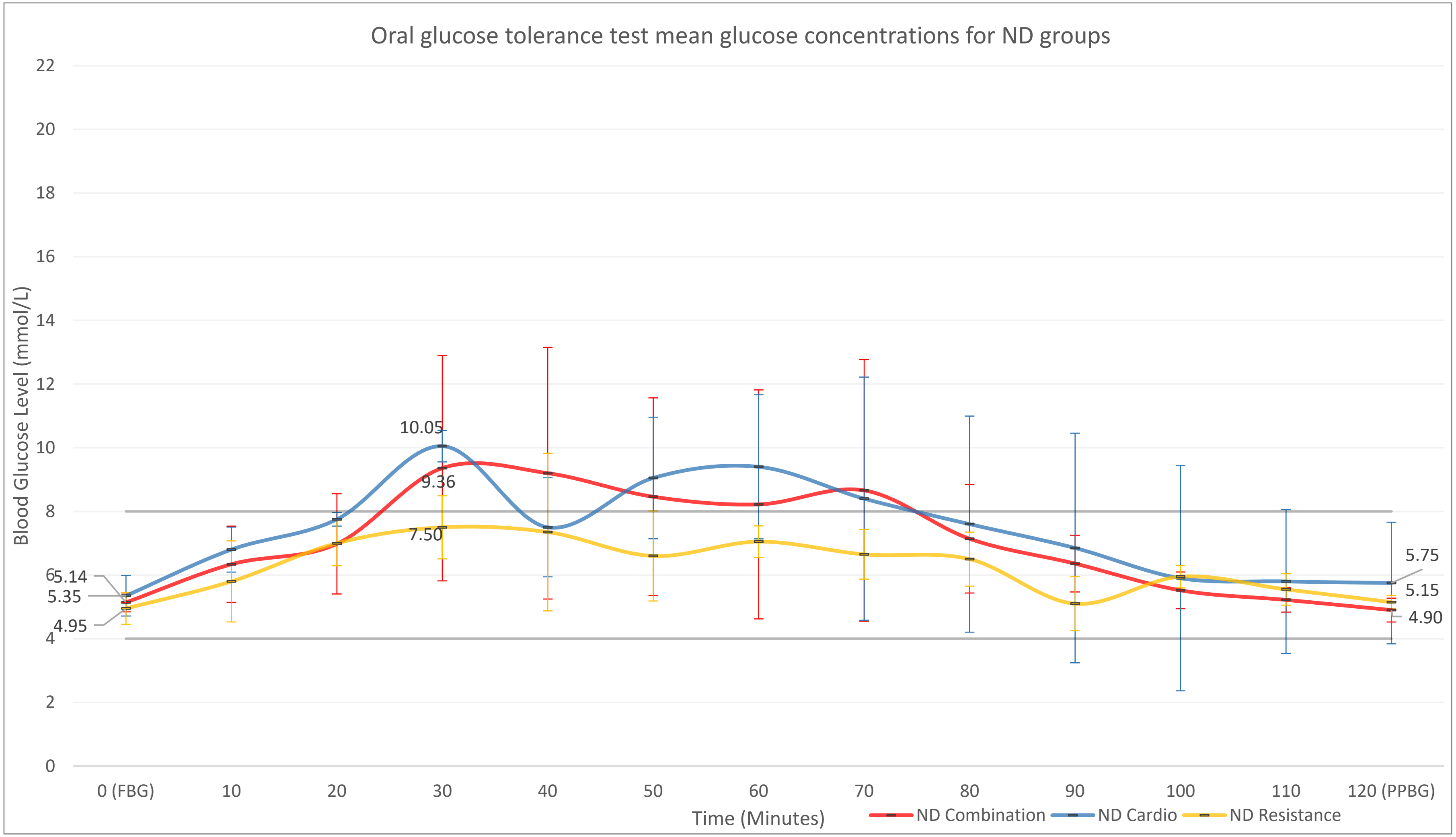

Figure 12, displays a line graph showing the three OGTTs mean and standard deviation results after the 12th exercise session for each ND volunteer groups. Normoglycaemia range is shown in bold.

The comparison of Figure 11 and Figure 12 for T2 and ND groups OGTT results after a structured exercise programme are as follows.

- All volunteer groups show a lower post prandial and fasting BG levels after 12 exercise sessions. This supports the theory that exercise increases BG control and therefore diabetic control.
- The T2 cardio group after 12 exercise sessions now have a mean post prandial BG level that is classified as pre-diabetic.
- After 12 exercises sessions both T2 and ND cardio groups have a lower post prandial BG level despite having a higher post prandial BG level after 1 exercise session.
- The T2 volunteers have shown a continuous improvement on all graphs whereas the ND groups improvement seems to slow down after the acute effects.
- The resistance groups seem to decrease BG levels the most effectively, this may be due to the increase muscle mass which means increased surface area and therefore improved BG control.

3.2.2 Fasting blood glucose

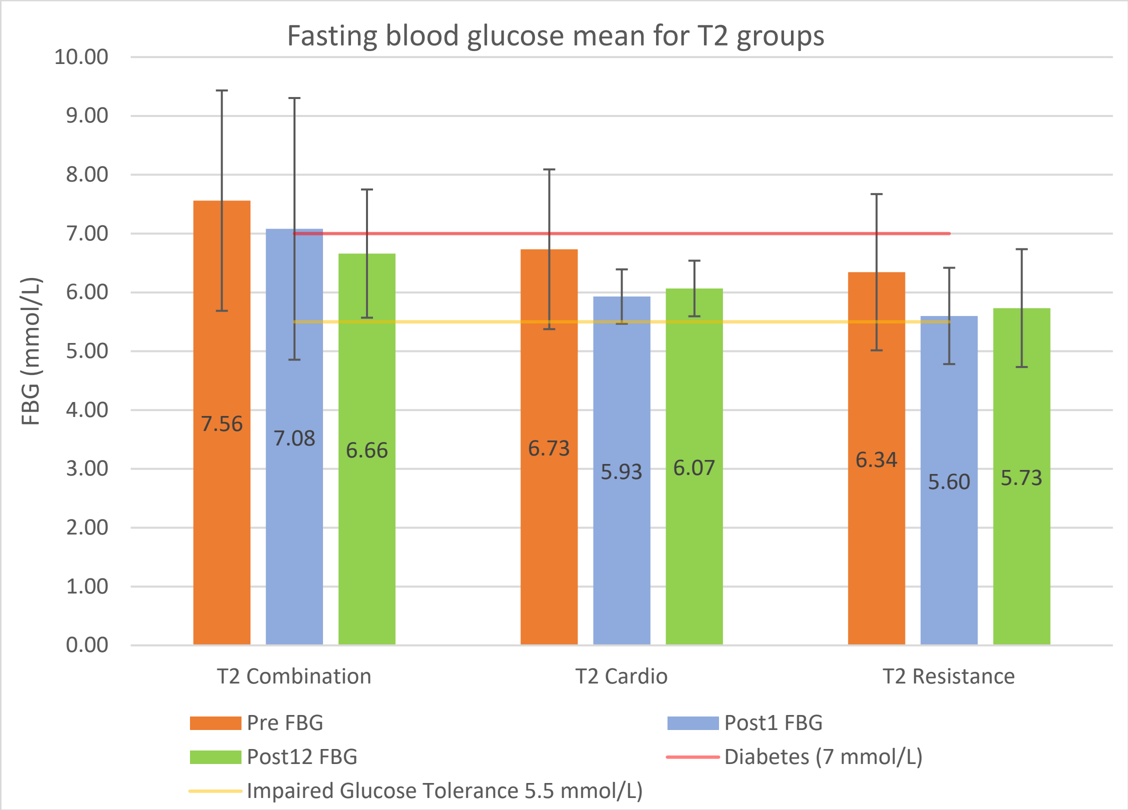

Figure 13, displays a column graph showing the pre, post1 and post12 exercise programme results for FBG (mmol/L) mean and standard deviation of each T2 volunteer control group. The red and yellow lines demonstrate the T2 diabetes mellitus and impaired glucose tolerance defined levels respectively according to NICE guidelines (NICE, 2012).

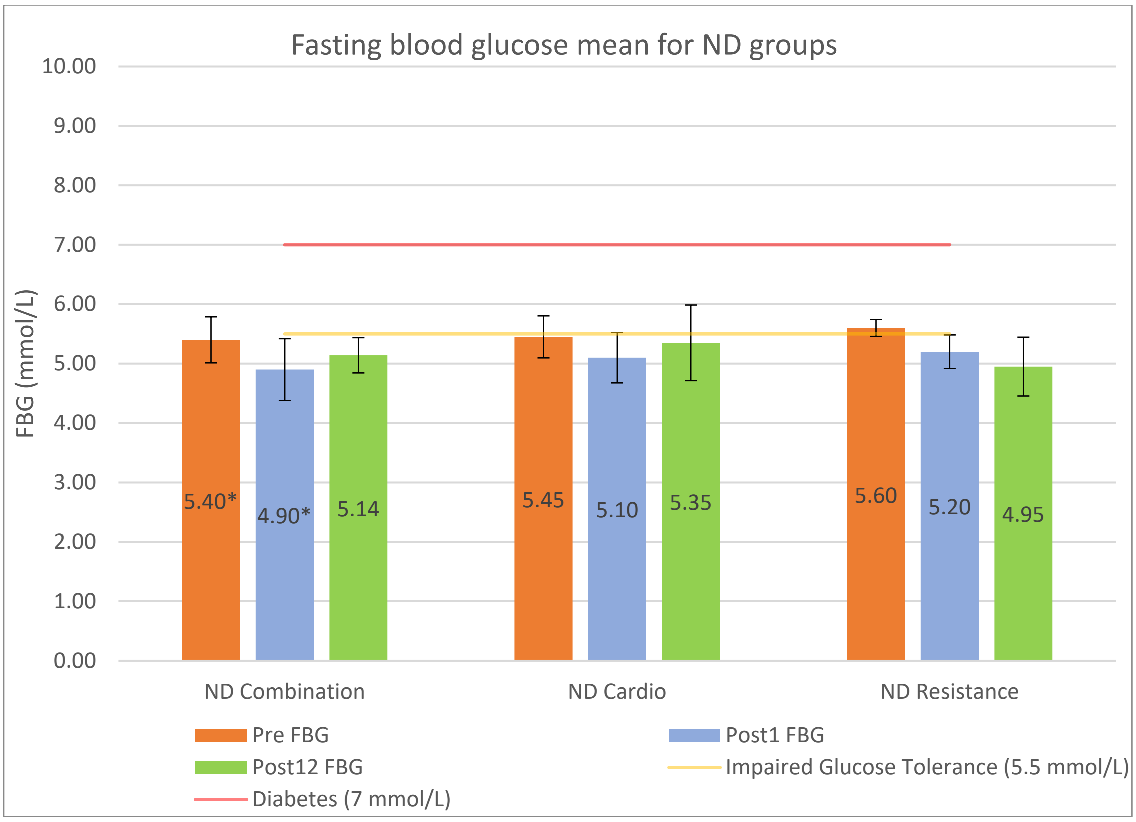

*Figure 14, displays a column graph showing the pre, post1 and post12 exercise programme results for FBG (mmol/L) mean and standard deviation of each ND volunteer control group. (*p < 0.05). The red and yellow lines demonstrate the T2 diabetes mellitus and impaired glucose tolerance defined levels respectively according to NICE guidelines (NICE, 2012).*

The comparison of Figure 13 and Figure 14 for T2 and ND FBG results are as follows.

- The ND combination group showed a statistically significant difference between pre and post1 FBG results with a p-value 0.024 which indicates this did not happen by chance.
- The acute results for ND combination group shown in Figure 14 have reduced from 5.40 to 4.9 mmol/L. however they went back up to 5.14 mmol/L after 12 exercise sessions.
- All groups showed a noticeable improvement of FBG levels after participating in the intervention however there was no significant overall reductions.

- In Figure 13 the T2 combination group shows a mean post12 FBG level below the diabetic classification. T2 combination group reduced from 7.56 to 6.66 mmol/L at the end of the structured exercise programme.

In 2015 Hariharasudhan et al. performed a study involving 80 T2DM volunteers. They were split into two groups. Both groups were treated with medication whilst one group was treated additionally with a set of exercises using a physio ball for a duration of 12 weeks. Subjects were 30-60 years old and exercised three times per week. Subjects performed three sets of five repetitions of each exercise. This exercise session is equivalent to this current study's T2 resistance exercise group. Hariharasudhan's study showed FBG decreased after resistance exercise by a mean value of 1.2 mmol/L whilst this current study showed a decrease of 0.61 mmol/L. Hariharasudhan's study may have shown a larger decrease due to the intervention length of 12 weeks. Hariharasudhan's study showed PPBG decreased after resistance exercise by a mean value of 1.5 mmol/L whilst the current study shows a PPBG mean reduction of 2.23 mmol/L. This current study shows a larger decrease in PPBG than Hariharasudhan's study despite being shorter. Hariharasudhan's study shows a HbA1c post mean lowered by 16 mmol/mol whilst this current study shows an increase of 0.77 mmol/mol in pre and post Hba1c results. This may be due to the extended duration of intervention seen in Hariharasudhan's study and increased frequency of exercise. Hariharasudhan's study showed waist circumference pre and post mean values decreased 2.33cm whilst in this current study the T2 resistance group mean showed an insignificant reduction of 0.27cm (Hariharasudhan and Varunkumar, 2015). This maybe be due to the duration of the current study being too short for significant waist circumference changes.

3.2.3 Post-prandial blood glucose

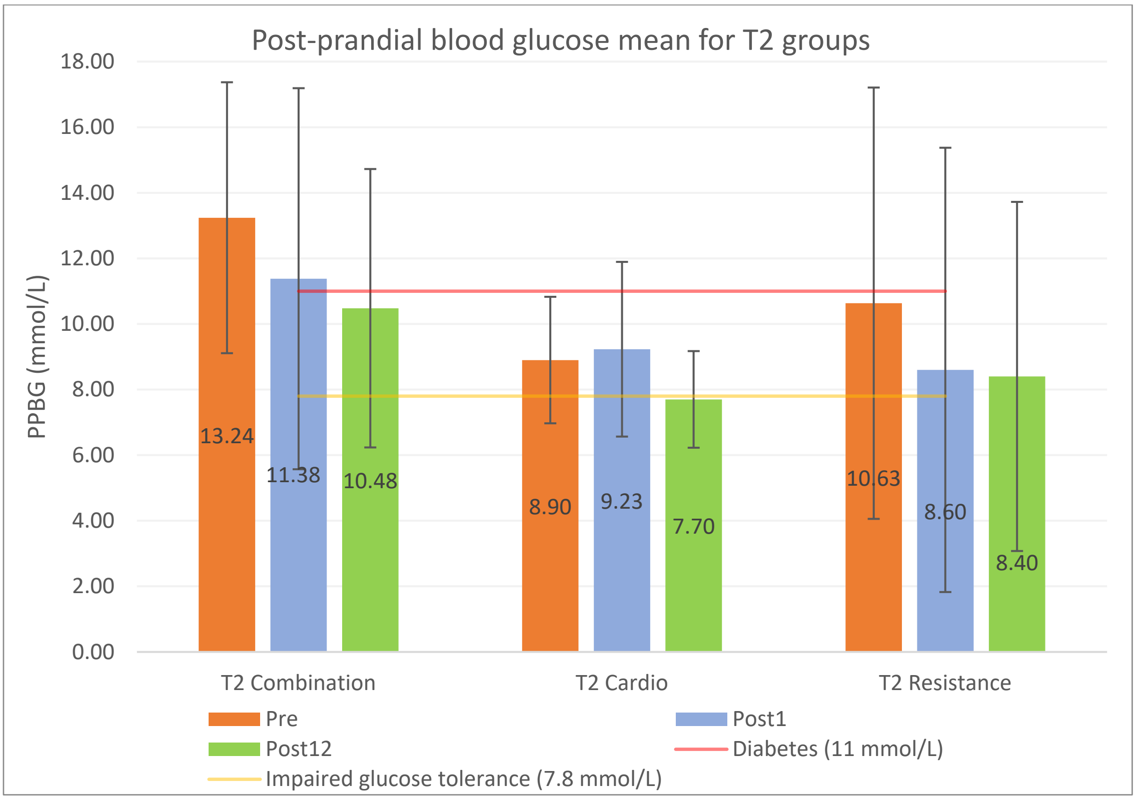

Figure 15, displays a column graph showing the pre, post1 and post12 exercise programme results for PPBG (mmol/L) mean and standard deviation of each T2 volunteer control group. Diabetic and impaired glucose tolerance guidelines showed as red and yellow lines (World Health Organisation, 2019).

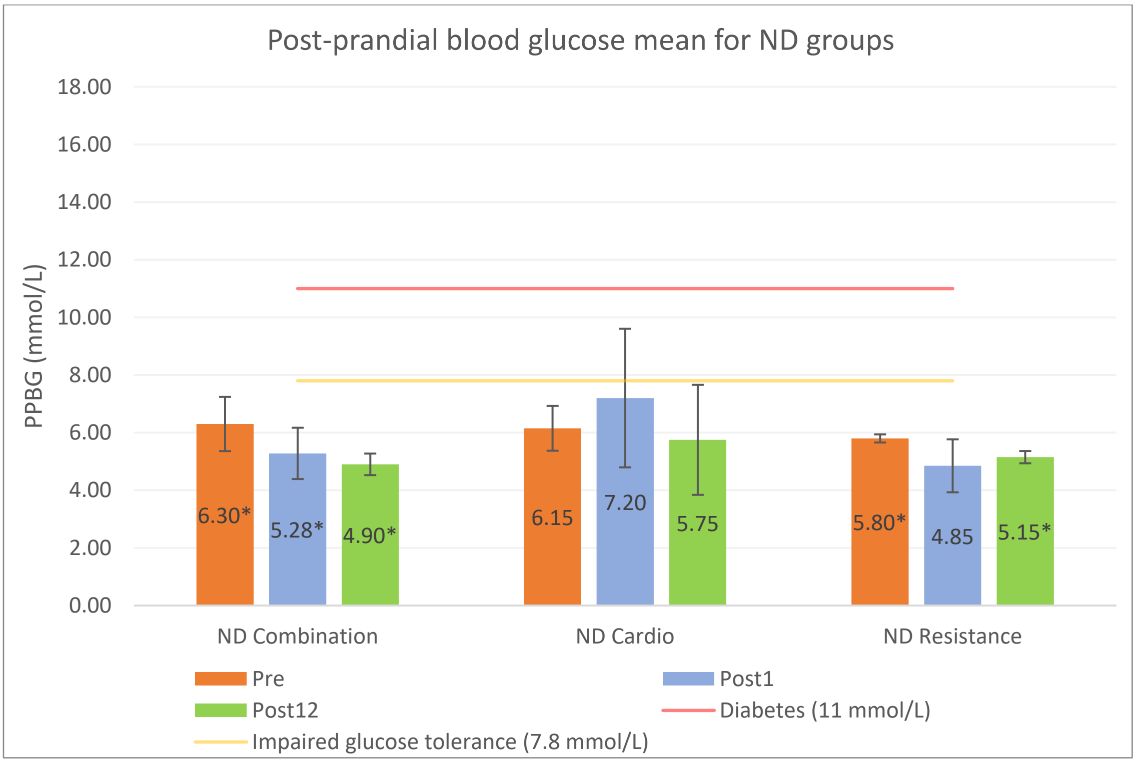

*Figure 16, displays a column graph showing the pre, post1 and post12 exercise programme results for PPBG (mmol/L) mean and standard deviation of each ND volunteer control group. (*p < 0.05). Diabetic and impaired glucose tolerance guidelines showed as red and yellow lines (World Health Organisation, 2019).*

The comparison of Figure 15 and Figure 16 for T2 and ND PPBG results are as follows.

- Both cardio groups showed an increase in PPBG after the first session, however both cardio groups then resulted in an overall decrease in PPBG.
- The T2 Cardio group was close to showing a statistically significant difference between pre and post12 with a p-value of 0.065.
- The ND combination group showed a statistically significant difference between pre and post 1 PPBG results with a p-value of 0.042.
- The ND combination also showed statistically significant difference between pre and post12 PPBG results with a p-value of 0.016.
- The ND resistance also showed statistically significant difference between pre and post 12 PPBG results with a p-value of 0.049.

3.2.4 OGTT area under curve

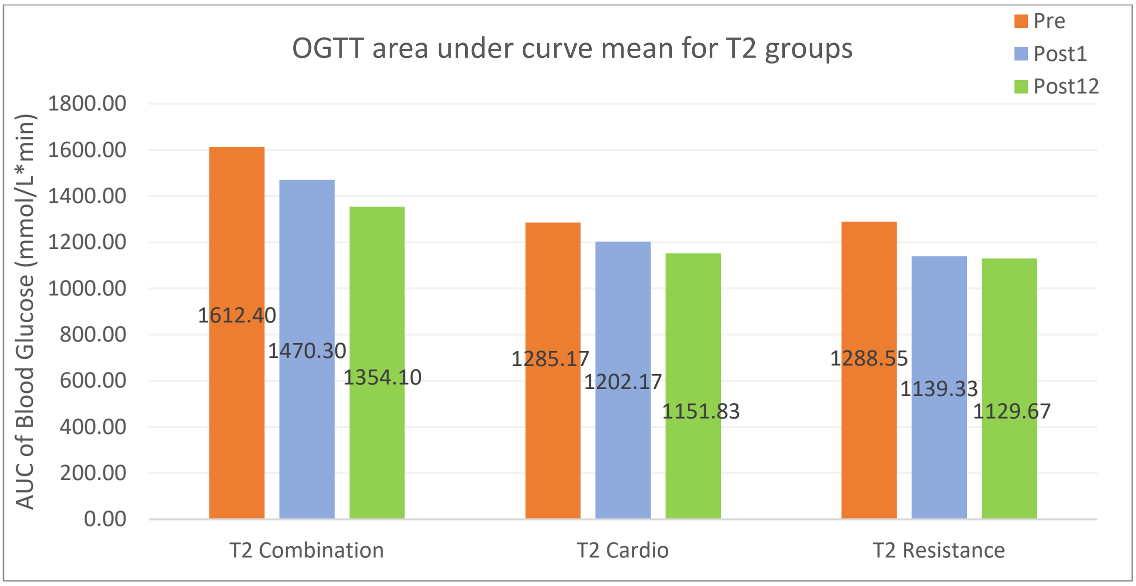

*Figure 17, displays a column graph showing the pre, post1 and post12 exercise programme results for OGTT area under curve (mmol/L*min) of each T2 volunteer control group.*

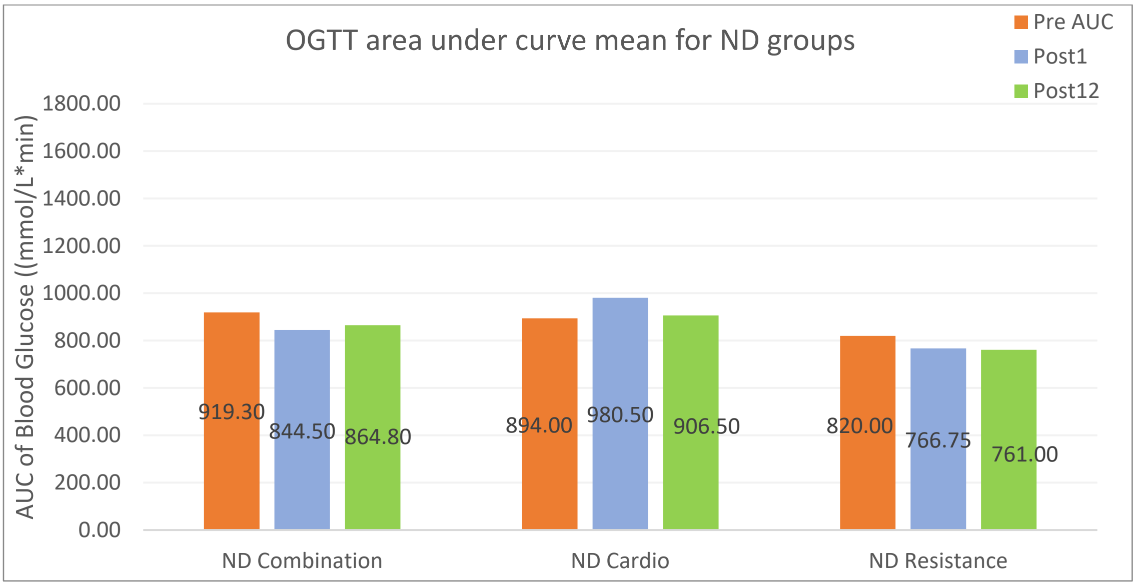

*Figure 18, displays a column graph showing the pre, post1 and post12 exercise programme results for OGTT area under curve (mmol/L*min) of each ND volunteer control group.*

OGTT area under the curve shows the OGTT curve in a numerical format which represents the improvement in BG control more clearly. The comparison of OGTT area under the curve in Figure 17 and Figure 18 for T2 and ND groups are as follows.

- The T2 combination group had the biggest decrease in OGTT area under the curve of 258.3 mmol/L*min.
- The T2 cardio and T2 resistance group had decreases of 133.34 and 158.88mmol/L*min respectively.
- The T2 groups in Figure 17 show a noticeably larger improvement in OGTT area under curve than the ND groups which may be because they had less room for health improvement than the T2 counterparts.
- The ND Cardio group was the only group not to show any improved OGTT area under curve in Figure 20.

3.2.5 OGTT time to peak

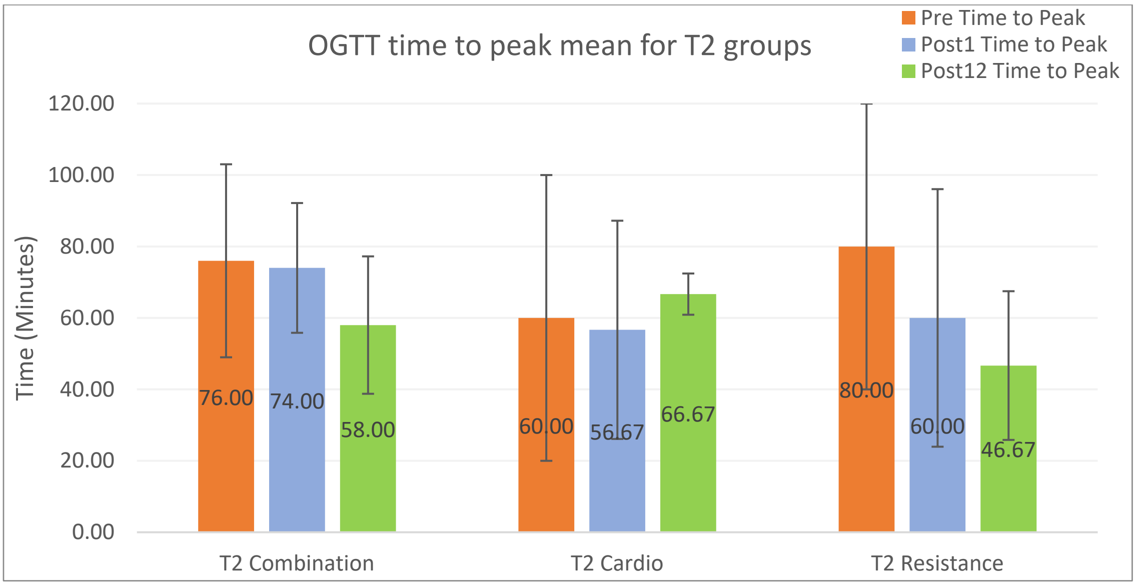

Figure 19, displays a column graph showing the pre, post1 and post12 exercise programme mean and standard deviation results for OGTT time to peak (minutes) of each T2 volunteer control group.

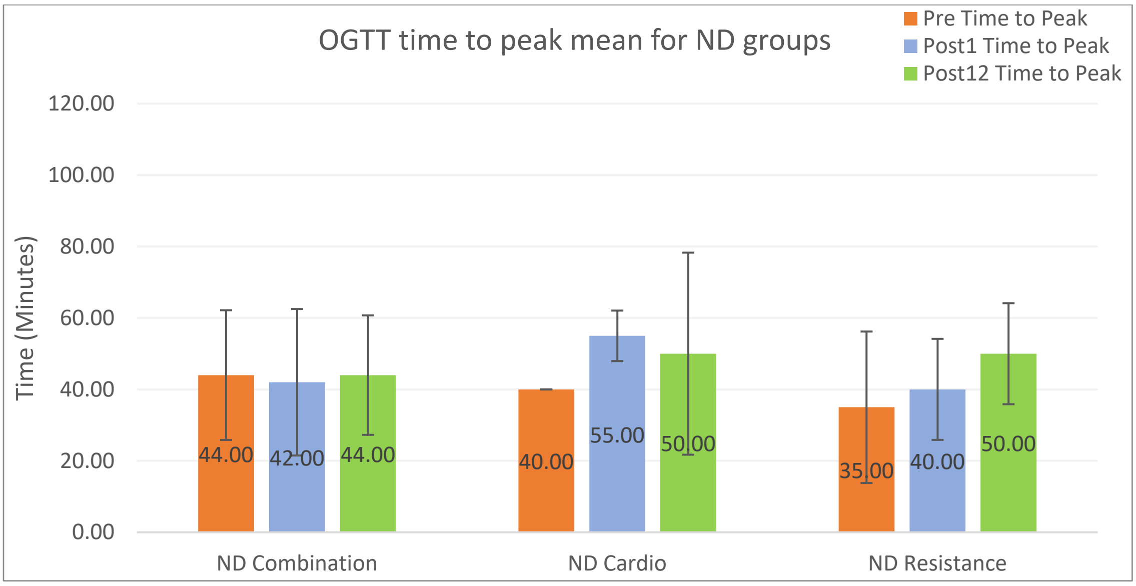

Figure 20, displays a column graph showing the pre, post1 and post12 exercise programme mean and standard deviation results for OGTT time to peak (minutes) of each ND volunteer control group.

The comparison of Figure 19 and Figure 20 for the T2 and ND groups mean time to peak results are as follows.

- In Figure 19 the T2 combination group has shown an improved time to peak from 76 to 58 minutes.
- The T2 resistance group has shown an improvement from 80 to 47 minutes time to peak. This indicates that a structured exercise programme involving resistance has improved BG control as it has taken less time to normalise BG levels.
- The T2 cardio group showed a slight increase from 60 to 67 minutes.
- The T2 groups have shown better improvements compared to the ND groups OGTT time to peak.

3.2.6 OGTT blood glucose peak

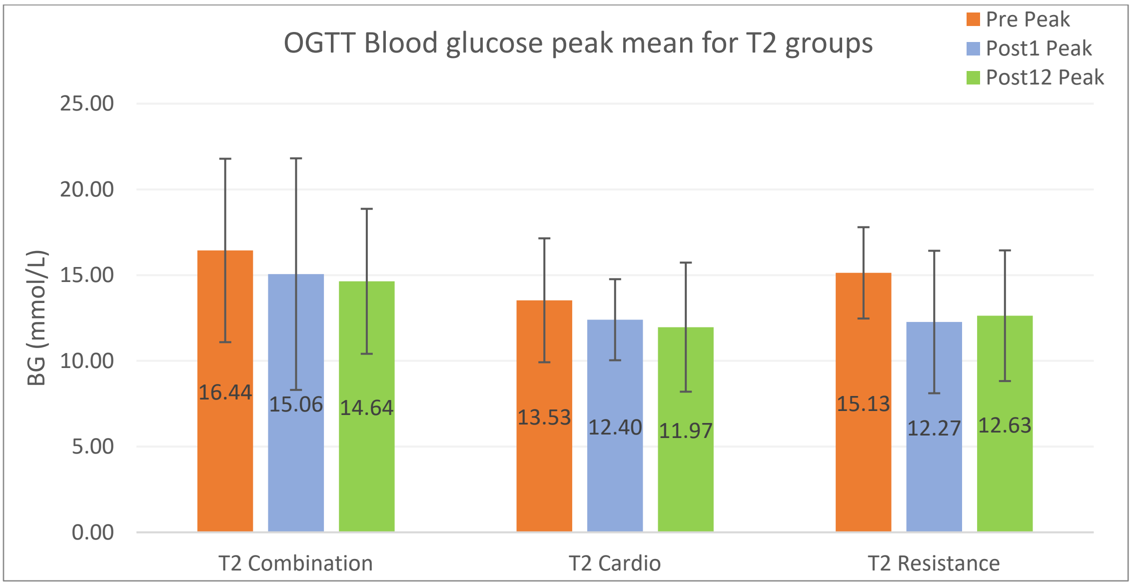

Figure 21, displays a column graph showing the pre, post1 and post12 exercise programme mean and standard deviation results for OGTT peak (mmol/L) of each T2 volunteer control group.

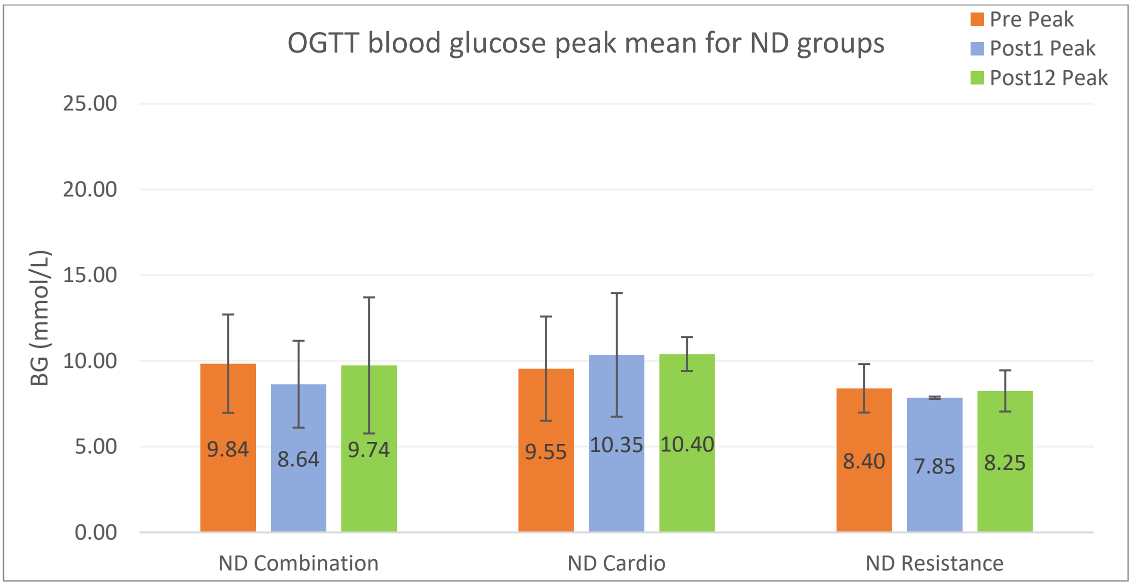

Figure 22, displays a column graph showing the pre, post1 and post12 exercise programme mean and standard deviation results for OGTT peak (mmol/L) of each ND volunteer control group.

The comparison of Figure 21 and Figure 22 for the T2 and ND groups mean OGTT peak results are as follows.

- In Figure 21 all T2 groups show a noticeable reduction in OGTT Peak. This shows that the T2 groups have an improved glucose tolerance after the structured exercise programme.
- Figure 22 ND combination and ND resistance groups shown a slight improvement in OGTT peak whereas ND cardio shown a slight increase in OGTT peak.

3.3 Baseline and chronic structured exercise programme results

Baseline and chronic results are shown in the graphs below as pre and post12 for HbA1c, BMI, waist, weight, peak expiratory flow rate, cholesterol, resting heart rate and blood pressure. These were recorded before the 1st exercise session and after the 12th exercise session which demonstrates the effects of the structured exercise programme.

3.3.1 HbA1c

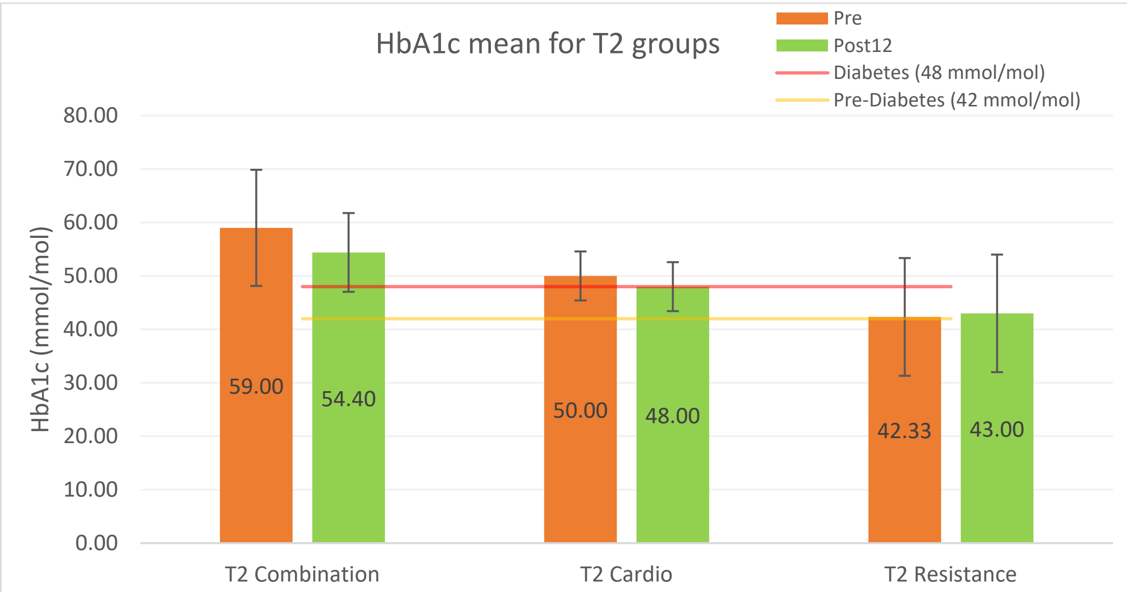

Figure 23, displays a column graph showing the pre and post exercise programme results for HbA1c (mmol/mol) mean and standard deviation of each T2 volunteer control group. The red and yellow lines demonstrate the T2DM and pre-diabetic defined levels respectively according to NICE guidelines (NICE, 2012).

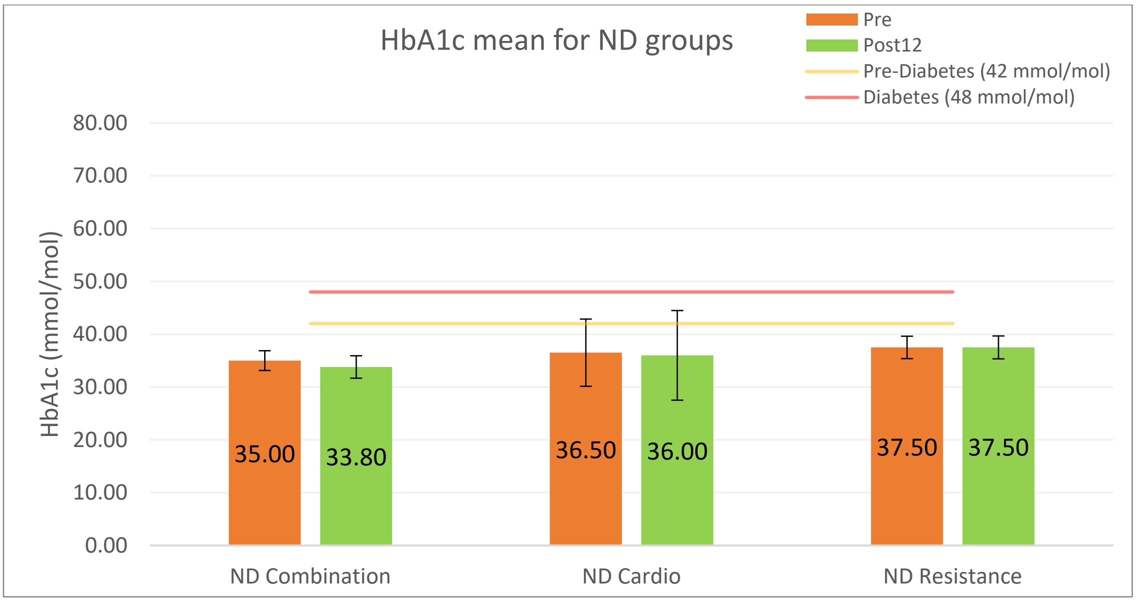

Figure 24, displays a column graph showing the pre and post exercise programmes results for HbA1c (mmol/mol) mean and standard deviation of each ND volunteer control group. The red and yellow lines demonstrate the T2DM and pre-diabetic defined levels respectively according to NICE guidelines (NICE, 2012).

Glycation is where glucose molecules bind to the haemoglobin modules found within red blood cells. This occurance can be used to assess the quantities of glucose concentrations within the body for the past three months. Therefore, a longer exercise programme duration may have shown a larger improvements.

The comparison of Figure 23 and Figure 24 for the T2 and ND groups HbA1c mean result after intervention are as follows.

- The starting HbA1c levels of the T2 groups in Figure 23 appear to be varied from 59 to 42.33 mmol/mol. It would have been better to group these volunteers so that each group has a more similar mean Hba1c starting baseline level.
- In Figure 23 both T2 combination and cardio groups show a reduction in HbA1c levels whereas the T2 resistance group shows a slight increase. T2 combination group reduced from 59 to 54.40mmol/L. T2 cardio group reduces from 50 to 48 mmol/L.

Increases in HbA1c levels can by due to resistance exercises, inducing glycogenolysis and gluconeogenesis which elevates BG concentration within the body during resistance training. In the short term the elevation in glucose levels may seem counterproductive. However, regular resistance training has shown to increase muscle mass. With this increase in muscle mass there would be more an increase in skeletal muscle cell size (hypertrophy) and an overall increase in the number of skeletal muscle cells (hyperplasia) which would potentially support the uptake of glucose causing a lowering of glucose concentration in the long term (Lixandrao et al., 2018).

The resistance groups may have not been as strict outside lab when at home with their diet than the other groups which may have affected these results. You would expect unhealthier T2 to reduce HbA1c more than healthier T2 or ND. This is shown where the T2 combination group has a larger decrease in HbA1c than T2 cardio group. This shows as the ND groups have a smaller reduction in HbA1c than T2.

The body will return to homeostatic balance with the negative compensation mechanisms. If HbA1c is within the normal range, then it is unlikely to improve or show significant change. Whereas if HbA1c is high then it is more likely to reduce. Corrective process is called homeostasis. If homeostasis is working properly then giving them some exercise will not affect as much. Whereas a little exercise form T2 will affect the body more to restore homeostasis.

Despite the T2 resistance group only including volunteers who have been diagnosed with T2DM the mean baseline HbA1c level of the group is in the pre-diabetic range.

After performing a paired t-test none of these HbA1c results shown in Figure 23 and Figure 24 show a statistically significant difference this may be due to a small sample size shown in Table 1. However, if this investigation was carried out again a power calculation would be used to calculate what suitable sample size is required to show a statistically significant difference. This would help determine if the implementation of participating in this structured exercise programme shows any benefits.

If the structured exercise programme had a longer duration HbA1c mean of the groups may have expressed a greater change in results. This is due to the life cycle of the red blood cell which 3 months. As the structured exercise only 2 months at most, there is not enough time to considerably affect the HbA1c readings.

In 2015 a study but Natesan et al. carried out a similar 8-week study which looked at engaging South Asian women with T2DM with exercise intervention. The sample size was 28 involving an age range of 18 to 85 year olds. It involved a one-hour Bollywood dance classes offered twice a week. The dance classes involved 10 minutes of warm-up, 30 minutes of Bollywood exercise, 15 minutes of muscle resistance and weight training, and 5 minutes of cool-down stretches. This exercise class is similar to this current studies combination exercise session.

HbA1c mean pre and post levels demonstrated show a decrease of 2.3 mmol/mol. Natesan's study correlates with this current study, the equivalent T2 combination group shows a reduction in HbA1c levels by 4.6 mmol/mol. This current study shows a larger decrease in HbA1c levels than Natesan's study despite the shorter duration of intervention. The intensity of exercise in this current study seems to have been higher than Natesan's. The exercise session duration and frequency were the same in both studies.

Participants attending at least 10 of 16 sessions had a statistically significant reduction in weight of 0.69 kg compared to those who attended fewer sessions with an increase of 0.86 kg. Natesan's study shows a smaller reduction in weight than this current study as the T2 combination group showed a reduction of 2.58 kg (Natesan et al., 2015). This current study may have had a larger reduction in weight due to a greater intensity of exercise within the session as the frequency was the same and exercise sessions were the same duration.

In 2014 Subramanian et al. performed a similar study with a sample size of 100. The sample size was split into two groups, control and experimental subjects. The control group was asked to maintain their inactive lifestyle whilst the experimental group were asked to perform aerobic exercises three days per week and resistance exercise two days per week using a physio ball for a period of 24-weeks. The aerobic exercise involved proper stretching, warming up, aerobic activity and cooling period. Resistance training involved 10 sets of exercises with an inflatable physio ball using bodyweight.

HbA1c decreased by 0.66% after 12-weeks and 1.33% after 24-weeks. This current study showed in the equivalent T2 combination group a decrease of 0.4% after 6 weeks. This correlates that combination exercise reduces HbA1c. Subramanian's study shows larger HbA1c decreases due to the increased frequency of exercise sessions and duration of intervention.

Waist circumference also showed decreases of 4.28 cm from the baseline value after 12-weeks and a decrease of 8 cm after 24-weeks. In This current study the equivalent T2 Combination group shows a decreased waist circumference after participation of a 6-week structured exercise programme of 4.5 cm. This correlates that a combination of cardio and resistance exercise decreases waist circumference. Subramanian's study shows larger decreases of waist circumference due to the longer intervention duration and increased frequency of exercise sessions (Subramanian et al., 2014).

In 2014 Subramanian et al. performed a similar study with a duration of 12 weeks involving 100 T2DM volunteers between the ages of 30-60 years old. The experimental group performed 10 exercises using the physio ball three times a week.

HbA1c in the experimental group reduced by 6.3 mmol/mol mean. In the equivalent T2 resistance group in this current study results experienced a slight increase in HbA1c mean values by 0.77 mmol/mol which opposes this current study's data. It may be suggested that the reason for this is due to the duration of the intervention which was 12 weeks compared with 6 weeks. Subramanian's volunteers also exercised more frequently three times a week compared with two times a week in this current study (Subramanian, Julius and Hariharasudan, 2014).

3.3.2 BMI

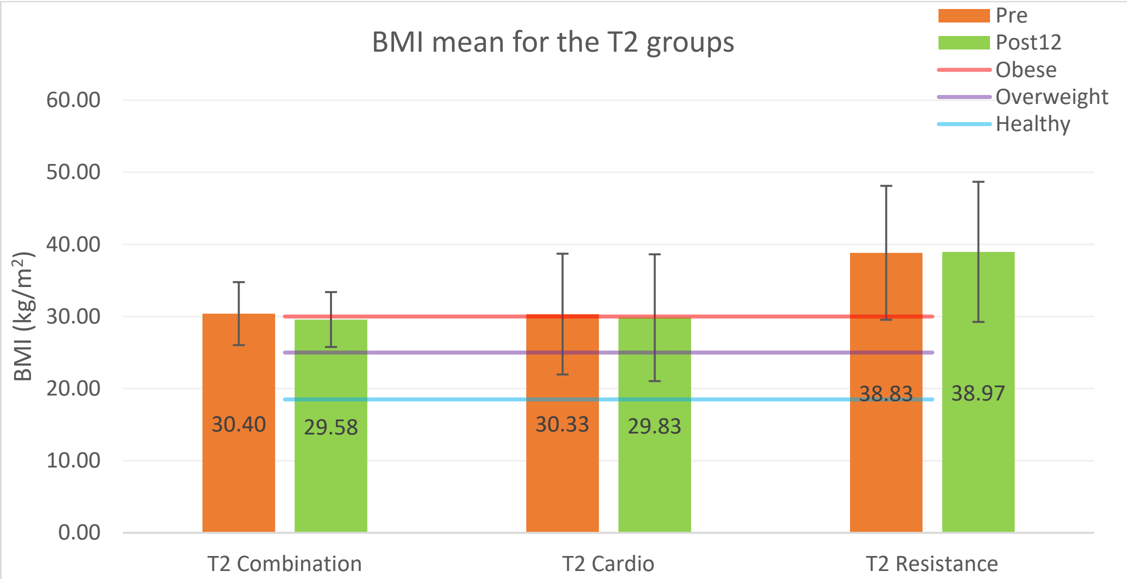

Figure 25, displays a column graph showing the pre and post exercise programme results for BMI mean and standard deviation of each T2 volunteer control group. The red, purple and blue lines show BMI levels respectively for the defined healthy, overweight and obese levels shown as recommended by the NHS (NHS, 2019c; Shields, 2006).

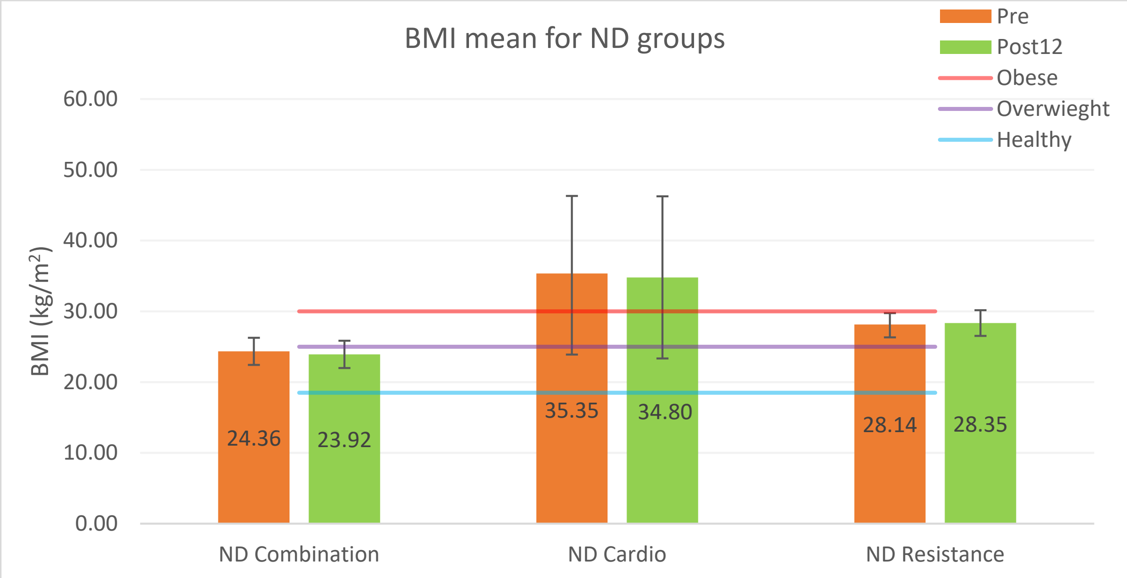

Figure 26, displays a column graph showing the pre and post exercise programme results for BMI mean and standard deviation of each T2 volunteer control group. The red, purple and blue lines show BMI levels respectively for the defined healthy, overweight and obese levels shown as recommended by the NHS (NHS, 2019c).

The comparison of Figure 25 and Figure 26 for the T2 and ND groups BMI mean results after intervention are as follows.

- In Figure 25, the T2 combination group mean BMI results were very close to showing a statistically significant difference from pre to post with a p-value of 0.054 and may have been if there were larger group numbers. Due to the low amount of sample size shown in Table 1 this number is not significant however if there were more volunteers in their respective groups a significant difference may have been shown.
- In Figure 25 and Figure 26 there was a slight reduction in BMI of T2 and ND combination and cardio groups. Whereas T2 resistance groups showed a slight increase in BMI whilst the ND resistance group showed no change in BMI. This may be caused by the increased muscle mass that is associated with resistance exercise.

It is interesting to see that the HbA1c decrease seen in volunteers has not transferred to a reduction in BMI. This could be due to the increase in muscle mass. However, as the study did not specify or record diet data the volunteers may have consumed more calories to compensate for hunger specifically the resistance exercise groups. Although, It has been debated that the BMI results can be inaccurate as it does not take into account muscle mass, body fat or bone density (Shah and Braverman, 2012; Gallagher et al., 1996).

Subramanian et al (2012) Recruited 60 T2DM aged 30 -60 years old. Randomly assigned to a supervised control group or moderate intensity resistance exercise using stability ball. The volunteers performed three sets of 5 repetitions, for each 10 exercises, in every session three times a week.

HbA1c mean values for the intervention group decreased by 6.1 mmol/mol whilst in this current study the equivalent T2 resistance group mean values experienced a 0.77 mmol/mol increase. This may be due to the increased frequency of exercise sessions in Subramanian's study.

BMI decreased by 1.60 in the mean whilst in this current study the BMI mean in T2 resistance group shows an increase of 0.14. This could be due to the increased frequency of exercise sessions in Subramanian's study (Subramanian and Venkatesan, 2012).

3.3.3 Weight

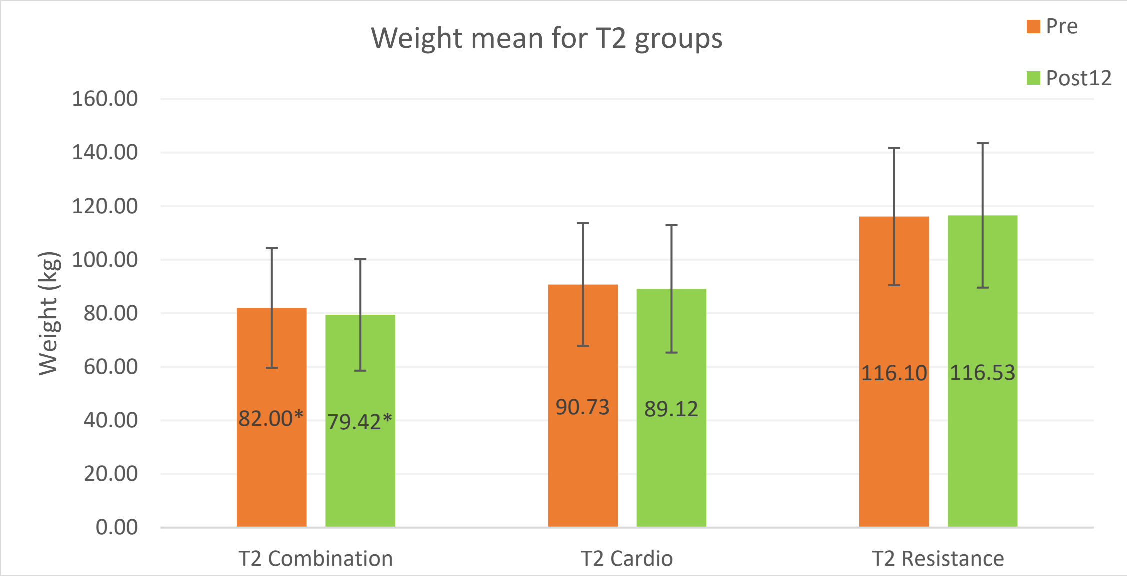

*Figure 27, displays a column graph showing the pre and post exercise programme mean and standard deviation results for weight (kg) of each T2 volunteer control group. (*p < 0.05)*

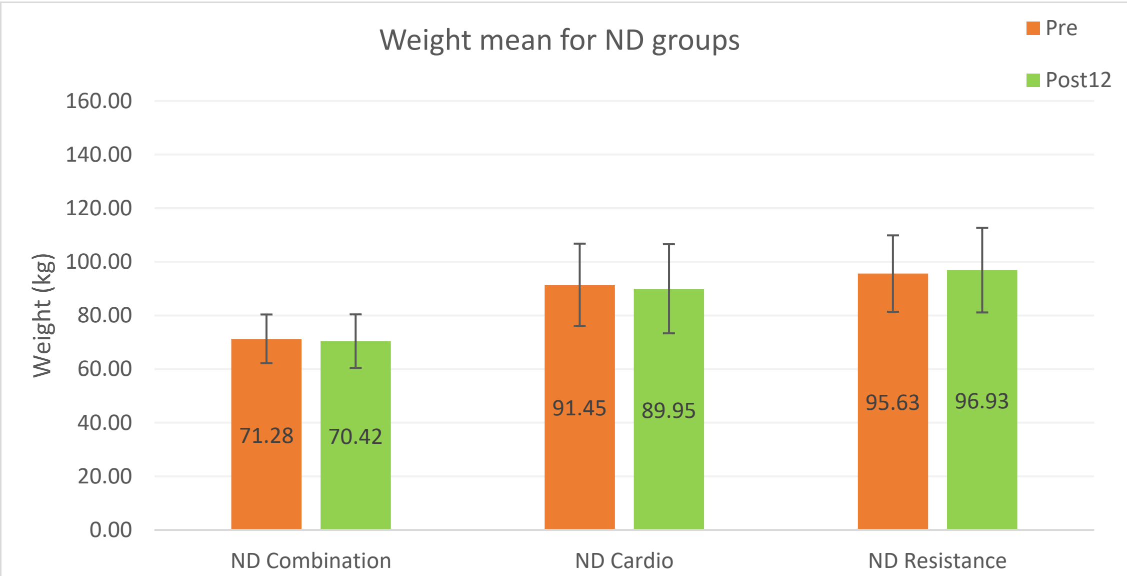

Figure 28, displays a column graph showing the pre and post exercise programme mean and standard deviation results for weight (kg) mean of each ND volunteer control group.

The comparison of Figure 27 and Figure 28 for the T2 and ND groups weight mean result after intervention are as follows.

- In Figure 27 the T2 combination group mean weight shows a statistically significant difference with a p-value of 0.049. T2 combination group reduced a mean weight from 82 to 79.42 kg. This shows that a combination of cardio and resistance exercise reduces weight most effectively.
- Both T2 and ND combination and cardio groups showed a decrease in weight. Whereas T2 and ND resistance groups show a slight increase in weight. This may be caused by the increased muscle mass that is associated with resistance exercise.

There was no large amount of weight lost. However, if the duration of the study was longer, they may have been a more significant change in their weight. The volunteers may have increased calorie intake due to hunger. This may have increased BG control by increasing muscle surface area which increases the amount of insulin and GLUT4 receptors (Mangine et al., 2015).

Exercise improved glucose transfer but it looks like calorie balance is similar, so they ended up maintaining weight. If a future study was done this study would extend the duration of the intervention from 6-weeks to 24-weeks, a recorded calorie diary would also be beneficial to determine the outcomes of the various types of exercise being performed.

There was a study of the effects of an 8-week weight loss programme involving dietary, exercise, multi-vitamin/mineral supplementation and behaviour modification components. The outcome of this study shows a decrease of 4.3 kg in women and 4.7 kg in men. BMI decreased significantly in women from 30.8 to 29.2 and also significantly in men from 30.0 to 28.5. The study had a longer intervention duration and had a larger cohort which are influencing factors when performing a paired t-test (Volek et al., 2002).

3.3.4 Waist circumference

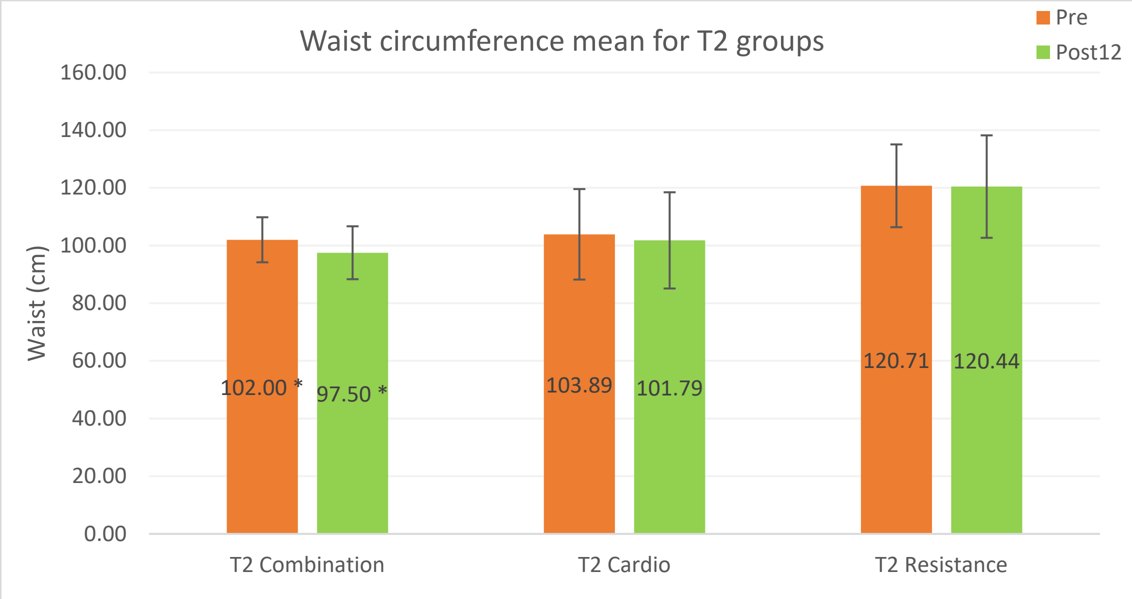

*Figure 29, displays a column graph showing the pre and post exercise programme results for waist circumference (cm) mean and standard deviation of each T2 volunteer control group. (*p < 0.05)*

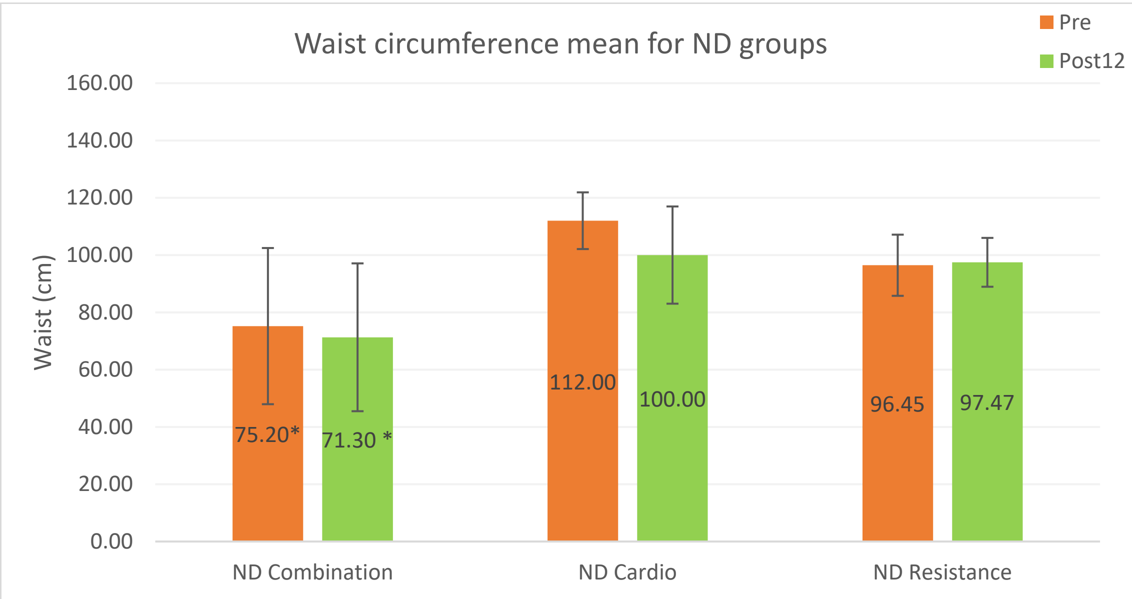

*Figure 30, displays a column graph showing the pre and post exercise programme results for waist circumference (cm) mean and standard deviation of each ND volunteer control group. (*p < 0.05)*

The comparison of Figure 29 and Figure 30 for the T2 and ND groups waist circumference mean results after intervention are as follows.

- In Figure 29 and Figure 30 both T2 and ND Combination programme control groups show a statistically significant difference from pre to post exercise programme waist circumference.
- In Figure 29 a 0.035 p-value is shown for the T2 Combination group which shows a statistically significant difference between pre and post exercise programme waist circumference results. T2 combination group waist mean reduced from 102 – 97.5 cm. This is the largest decrease of 4.5 cm.
- In Figure 30 a 0.008 p-value is shown for the ND Combination group which shows a statistically significant difference between pre and post exercise programme waist circumference results. ND combination group reduced from 75.2 to 71.3 cm.
- All groups showed a reduction in waist circumference mean except ND resistance group in Figure 30 which had a small increase from 96.45 to 97.47 cm. Muscle mass increased by resistance exercise may be the reason that caused the increase in waist circumference.

3.3.5 Peak expiratory flow rate

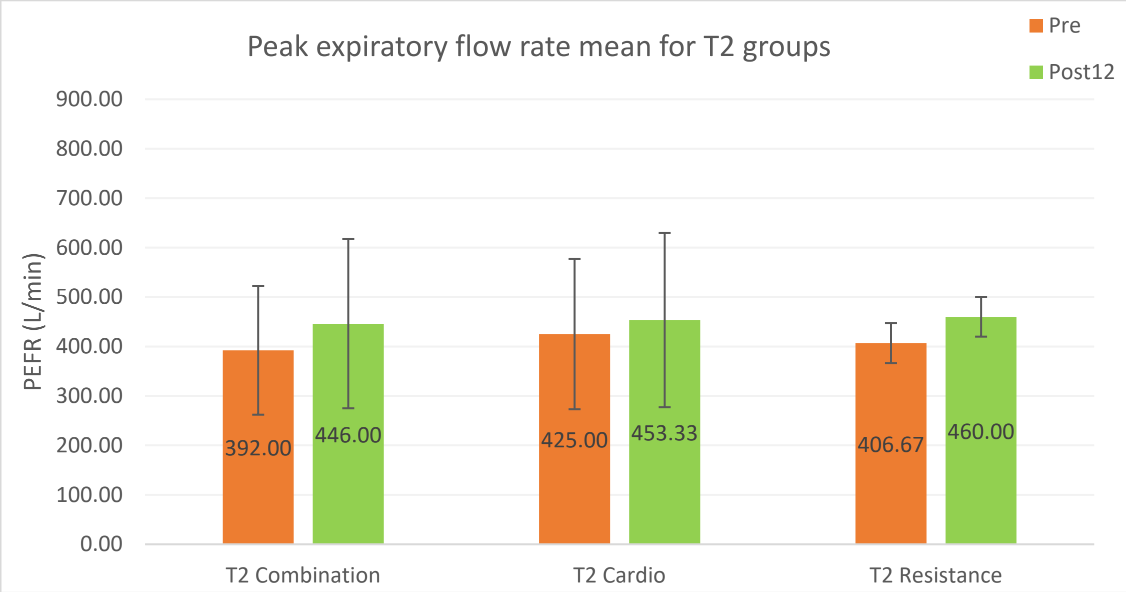

Figure 31, displays a column graph showing the pre and post exercise programme results for peak expiratory flow rate (L/min) mean and standard deviation of each T2 volunteer control group.

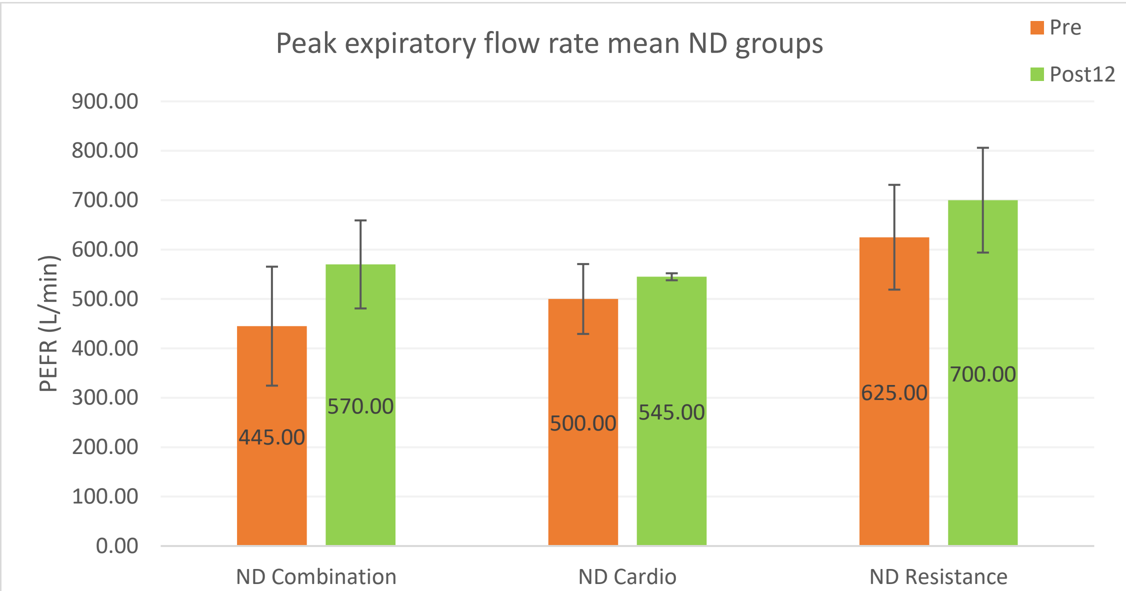

Figure 32, displays a column graph showing the pre and post exercise programme results for peak expiratory flow rate (L/min) mean and standard deviation of each ND volunteer control group.

The comparison of Figure 31 and Figure 32 for the T2 and ND groups Peak expiratory flow mean result after intervention are as follows.

- All groups showed a noticeable improvement in peak expiratory flow. This shows that a structured exercise programme increases peak expiratory flow rate in volunteers.
- In Figure 32 ND combination had the largest increase from 445 to 570 L/min. The ND combination were very close to showing statistical significance between pre and post results with a p-value of 0.058.
- Surprisingly the T2 and ND cardio groups show the smallest increases of peak expiratory flow rate. This may be due to the small sample size shown in Table 1.

3.3.6 Resting heart rate

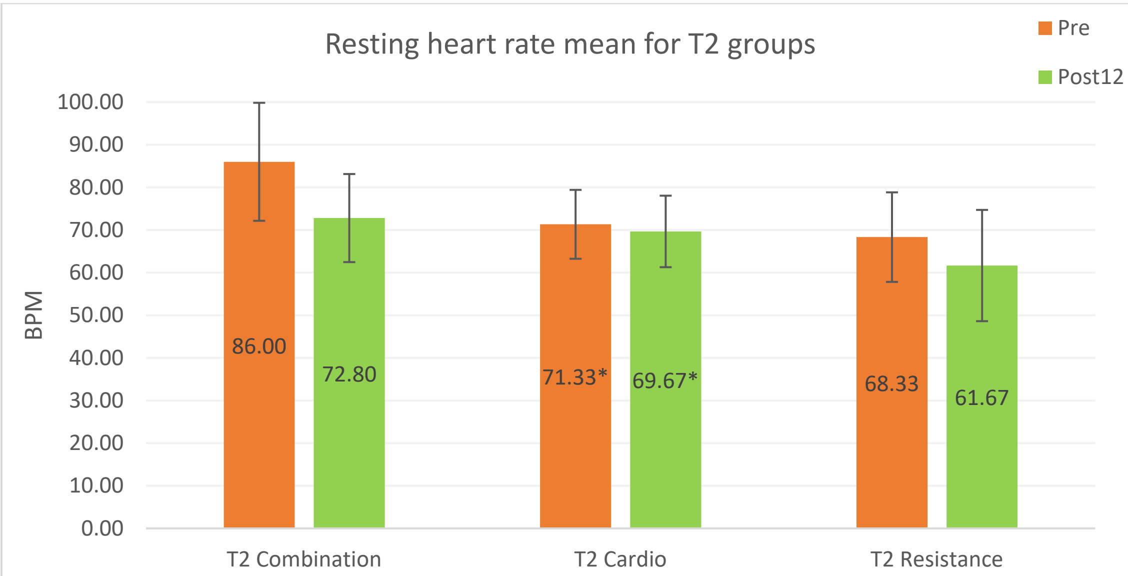

*Figure 33, displays a column graph showing the pre and post exercise programme results for resting HR (BPM) mean and standard deviation of each T2 volunteer control group. (*p < 0.05)*

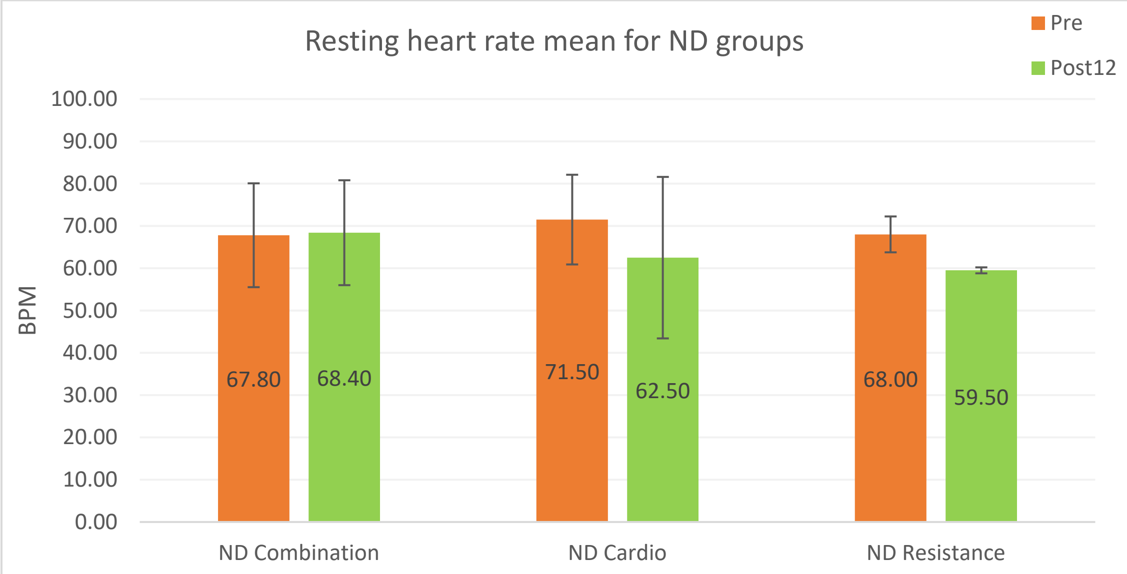

Figure 34, displays a column graph showing the pre and post exercise programme results for Resting HR (BPM) mean and standard deviation of each ND volunteer control group.

The comparison of Figure 33 and Figure 34 for the T2 and ND groups resting heart rate mean result after intervention are as follows.

- Figure 33 shows there was a statistically significant difference between pre and post resting HR results in the T2 cardio with a p-value of 0.038. T2 cardio group mean reduced from 71.33 to 69.37 BPM.
- The T2 combination group shown in Figure 33 shows the greatest decrease in resting HR mean from 86 to 72.8 BPM.
- In Figure 34 Resistance ND group shows a noticeably large reduction in resting HR mean from 68 to 59.5 BPM.
- The ND combination group was the only group to increase resting HR mean from 67.8 to 68.4 BPM. The initial resting HR was considered normal to at the start at the intervention so it would be difficult to show significant improvement.

3.3.7 Total cholesterol

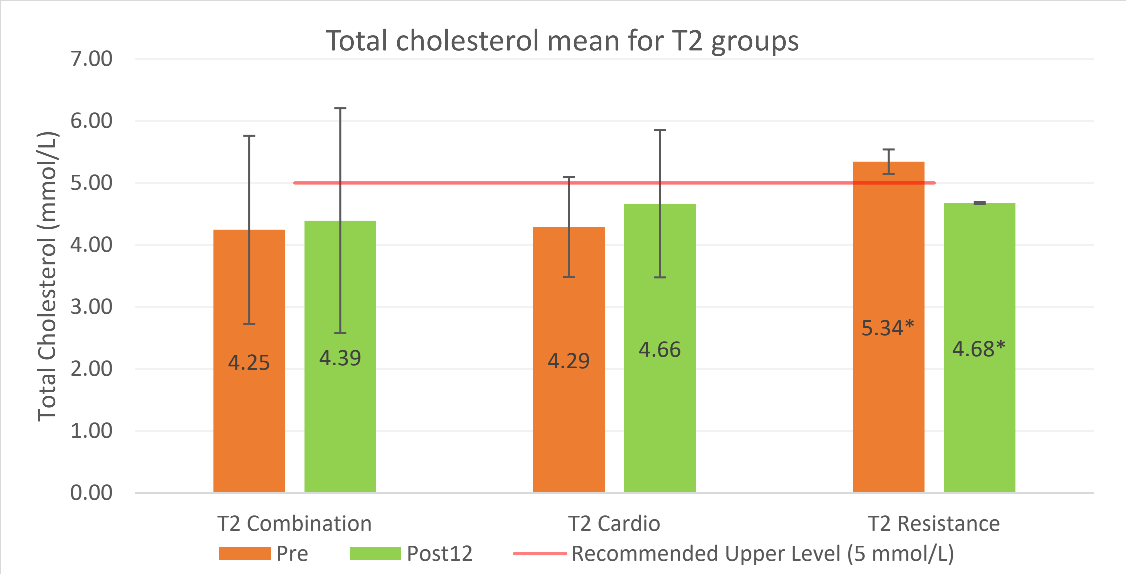

*Figure 35, displays a column graph showing the pre and post exercise programme results for total cholesterol (mmol/L) mean and standard deviation of each T2 volunteer control group. (*p < 0.05). NHS recommended healthy levels shown (NHS, 2019a).*

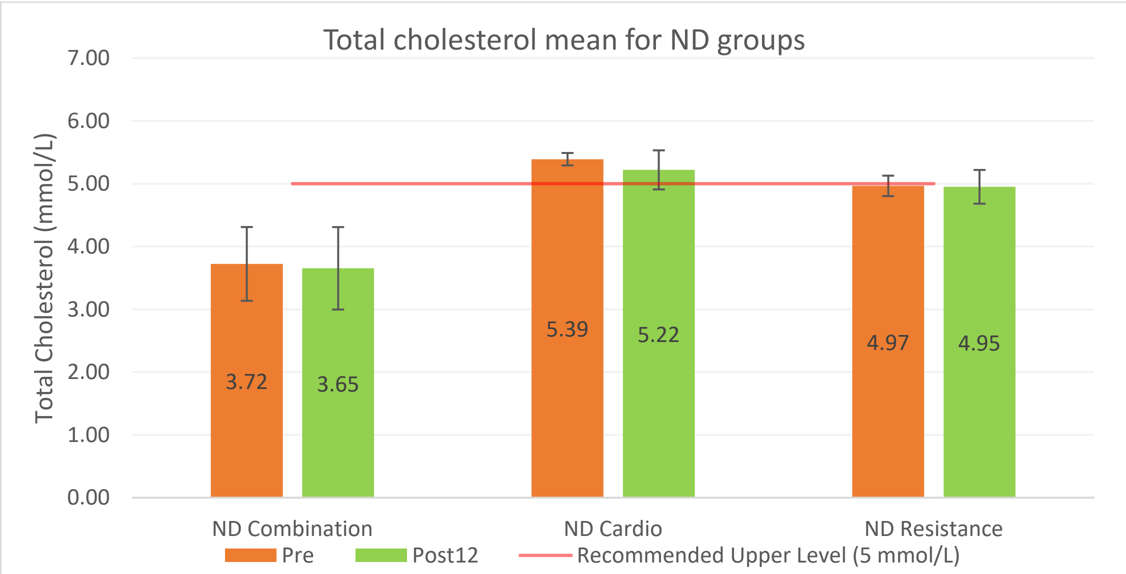

Figure 36, displays a column graph showing the pre and post exercise programme results for total cholesterol (mmol/L) mean and standard deviation of each ND volunteer control group. NHS recommended healthy levels shown (NHS, 2019a).

The comparison of Figure 35 and Figure 36 for the T2 and ND groups total cholesterol mean result after intervention are as follows.

- In Figure 35 the T2 resistance group showed statistically significant difference of total cholesterol results between pre to post exercise programme with a p-value of 0.031. T2 resistance group showed the largest decrease of total cholesterol mean from 5.34-4.68 mmol/L which is under the recommended healthy level of below 5mmol/L.
- In Figure 35 T2 combination and cardio groups both showed an increase in total cholesterol mean. T2 combination increased from 4.25 to 4.39 mmol/L. T2 cardio group increased from 4.29 to 4.66 mmol/L.

In 2009 Arora et al. performed a similar study with a cohort size of 30 adults with T2DM. Subjects were split into two groups. A progressive resistance training group involved 3 sets of 10 repetitions for 7 exercises where training started at 60% of 1RM and then progressed to 100% of 1RM during the 8-week training period, this group is similar to this current studies T2 resistance group. In the aerobic exercise group subjects performed walking as the aerobic exercise for 30 minutes per day three times a week for 8 weeks, which is similar to this current studies T2 cardio group.

Total cholesterol decreased from 4.86 to 4.22 mmol/L in the PRT group whilst in this current study the equivalent T2 resistance group experienced a total cholesterol mean decrease from 5.34 to 4.68 mmol/L which shows correlating results.

Total cholesterol decreased from 4.73 to 4.45 mmol/L in the AE group whilst an increase from 4.29 to 4.66 mmol/L was shown in this current study's equivalent T2 cardio group. This may be due to the higher frequency of exercise sessions performed by Aurora volunteers or the 2-week longer duration of intervention.

Hba1c decreased from 59.2 to 44.6 mmol/mol in the PRT group whilst in this current study the equivalent group of T2 resistance show HbA1c results slightly increase from 42.33 to 43mmol/mol. This could be due the intensity of the progressive resistance training group which increased to 100% by the end of Arora's study. Arora's PRT group also had 2 extra weeks of intervention duration which would particularly benefit HbA1c results due to the 3-month lifecycle of the red blood cell.

HbA1c decreased from 65.1 to 49.3 mmol/mol in AE group which shows a larger reduction in HbA1c mean levels than this current study's equivalent T2 cardio group which shows a decrease from 50 to 48 mmol/mol. This could be due to the 2-week longer duration of intervention. This could also be due to the higher frequency of exercise performed.

The BMI score from Arora's study did not significantly change during the 8 weeks. Which is also what is seen between this current study's BMI mean score before and after intervention (Arora, Shenoy and Sandhu, 2009).

3.3.8 High-density lipoproteins

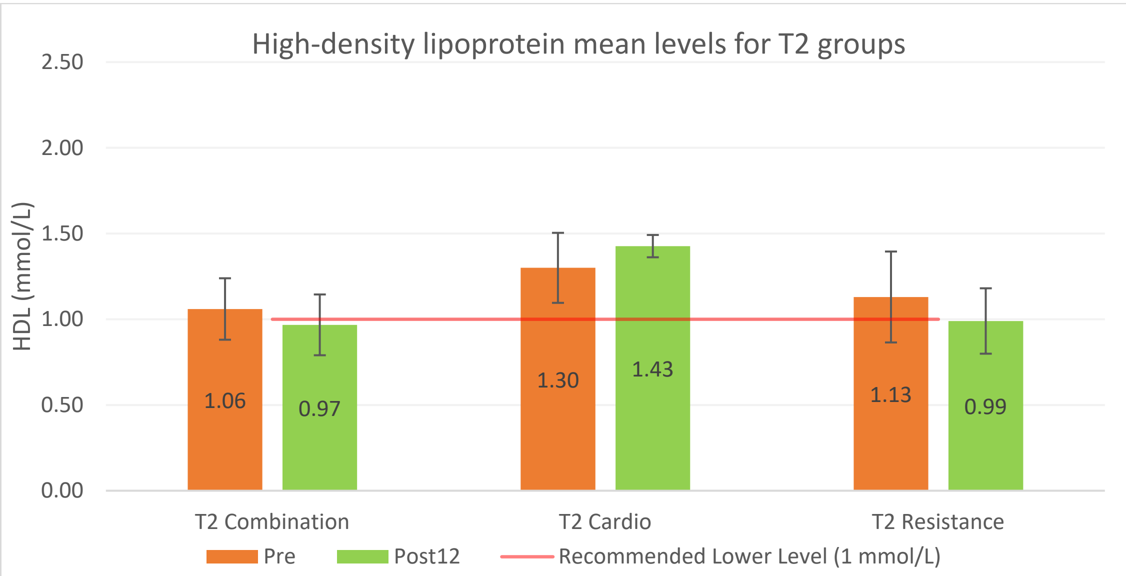

Figure 37, displays a column graph showing the pre and post exercise programme results for HDL (mmol/L) mean and standard deviation of each T2 volunteer control group. NHS recommended healthy level shown (NHS, 2019a).

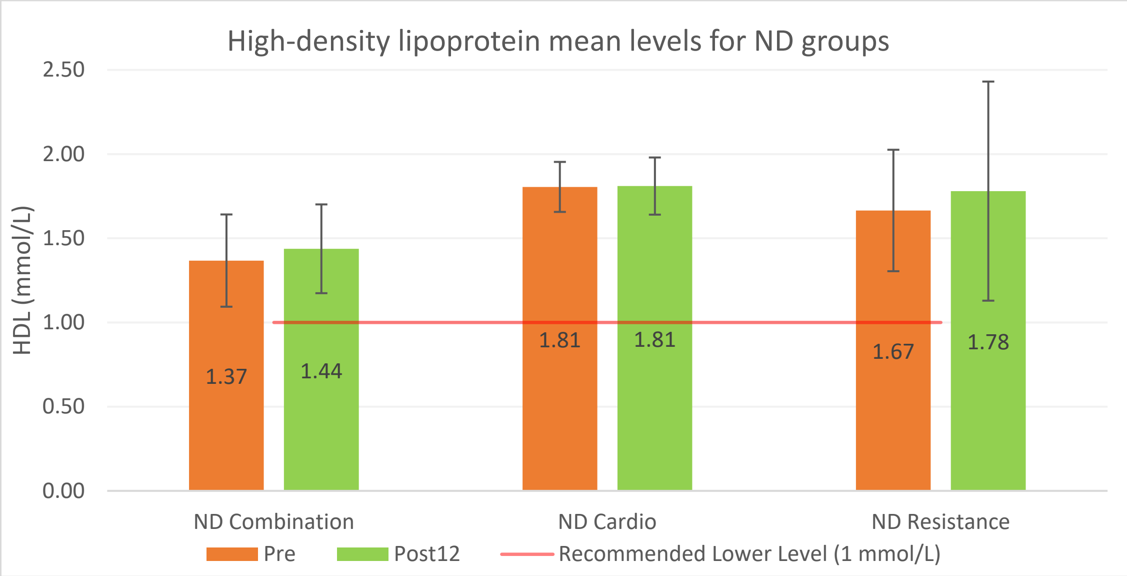

Figure 38, displays a column graph showing the pre and post exercise programme results for HDL (mmol/L) mean and standard deviation of each ND volunteer control group. NHS recommended healthy level shown (NHS, 2019a).

The comparison of Figure 37 and Figure 38 for the T2 and ND groups HDL mean result after intervention are as follows.

- All high-density lipid mean baselines were above the recommended lower level but T2 and combination and resistance after a structured exercise programme resulted in a slight decrease which brought their values within the recommended ranges.
- In Figure 37 T2 combination shown a decrease of high-density lipids mean from 1.06 to 0.97 mmol/L after taking part in a structured exercise programme. T2 resistance group shows a decrease in high-density lipids from 1.13 to 0.99 mmol/L from pre – post structured exercise programme.

In 2012 Hameed et al. performed a similar study involving 48 untrained subjects. The intervention duration was 8 weeks involving progressive resistance exercise or control programme. The PRT group undertook 5 exercises using weight machines at an intensity of 60% 1RM and after 4 weeks the intensity increased to 70% of 1RM. They performed 3 sets of 10 repetitions for each exercise.

HDL mean for the PRT group in Hameed's study increased by 0.11 mmol/L whilst in this current study the T2 resistance group shows a decrease of 0.14 mmol/L. As HDL is increased by various diet factors such as magnesium supplements, removing trans fatty acids from the diet or decreasing intake of simple carbohydrates. As diet was not recorded in this current study these could be the factors that effected the opposed results.

Hameed's study experienced a reduction of 6.8 mmol/mol in HbA1c means for the PRT group from before to after intervention. Hameed's study opposes this current study which experienced an increase in the HbA1c mean of the T2 resistance group. This could be due to the longer intervention of 8 weeks and more frequent exercises sessions in Hameed's study.

Hameed's study experienced an increase in the weight mean of 0.25 kg which correlates with this current study which showed an increase of 0.43 kg in weight mean of the equivalent T2 resistance group. This current study shows a slightly larger decrease in weight mean.

The waist circumference mean for the PRT group decreased by 1.86 cm in Hameed's study whilst in this current study the T2 resistance group show a waist circumference mean decrease of 0.27 cm. Hameed's study shows much larger decreases in waist circumference this may be due to the more frequent exercise session and longer intervention duration in Hameed's study (Hameed et al., 2012).

3.3.9 Triglycerides

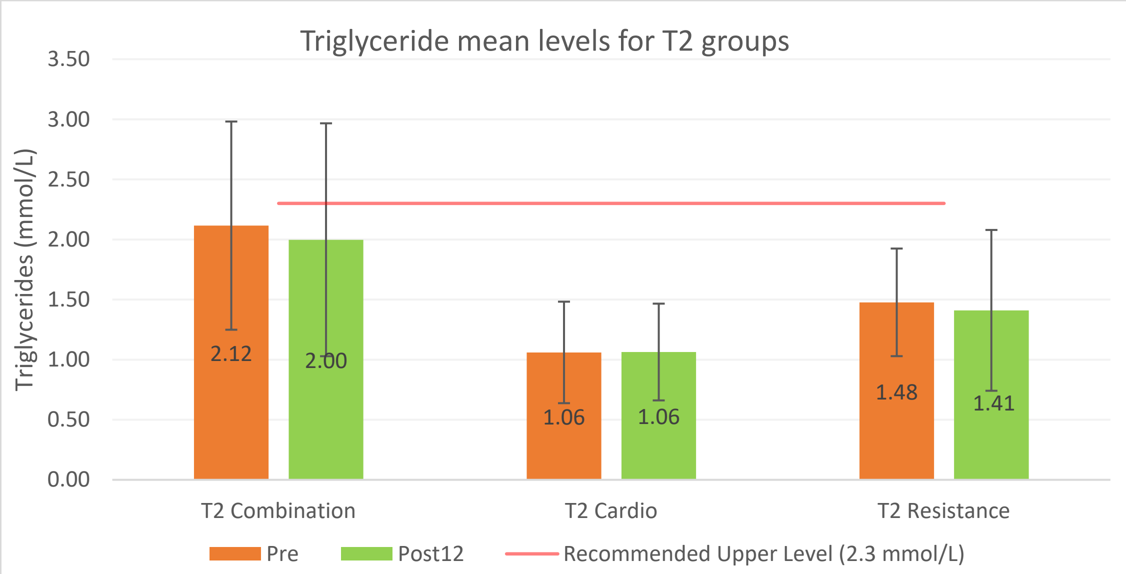

Figure 39, displays a column graph showing the pre and post exercise programme results for triglycerides (mmol/L) mean and standard deviation of each T2 volunteer control group. NHS recommended healthy level shown (NHS, 2019a).

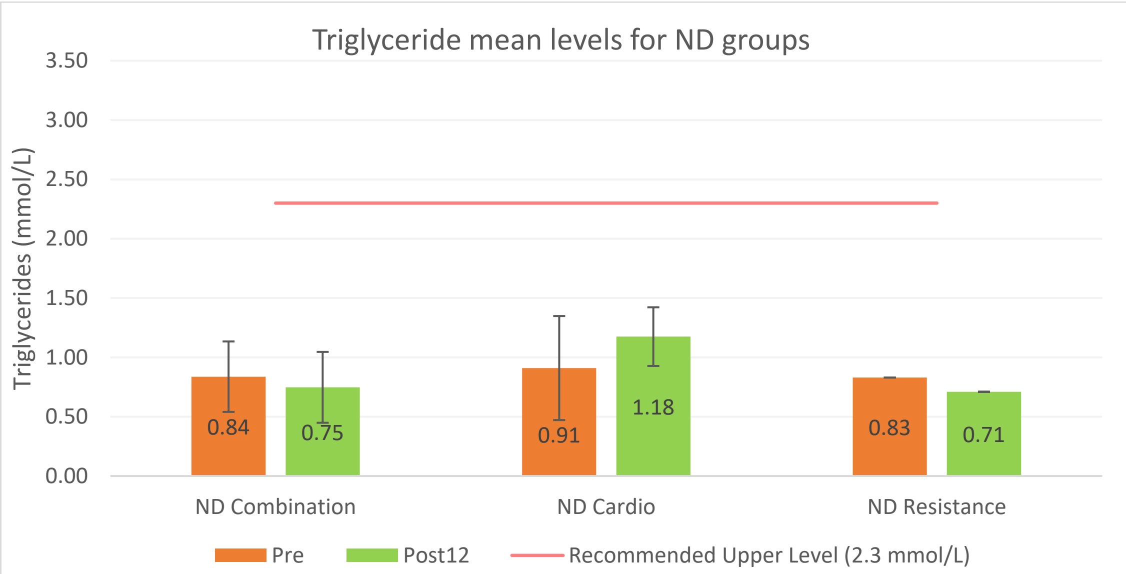

Figure 40, displays a column graph showing the pre and post exercise programme results for triglycerides (mmol/L) mean and standard deviation of each ND volunteer control group. NHS recommended healthy level shown (NHS, 2019a).

The comparison of Figure 39 and Figure 40 for the T2 and ND groups triglyceride levels for mean result after intervention are as follows.

- In Figure 39 T2 combination group triglyceride mean reduced from 2.12 to 2.00 mmol/L whilst T2 resistance reduced from 1.48 to 1.41 mmol/L. T2 cardio stayed the same at 1.06 mmol/L.
- In Figure 40 ND combination and ND resistance triglyceride levels decreased whilst ND Cardio increased from 0.91 to 1.18 mmol/L.
- Both cardio groups failed to show a reduction in triglyceride levels indicating. Interestingly the combination and resistance groups for both T2 and ND cohorts demonstrated a reduction in triglyceride levels compared to their cardio based intervention counterparts.

3.3.10 Low-density lipoproteins

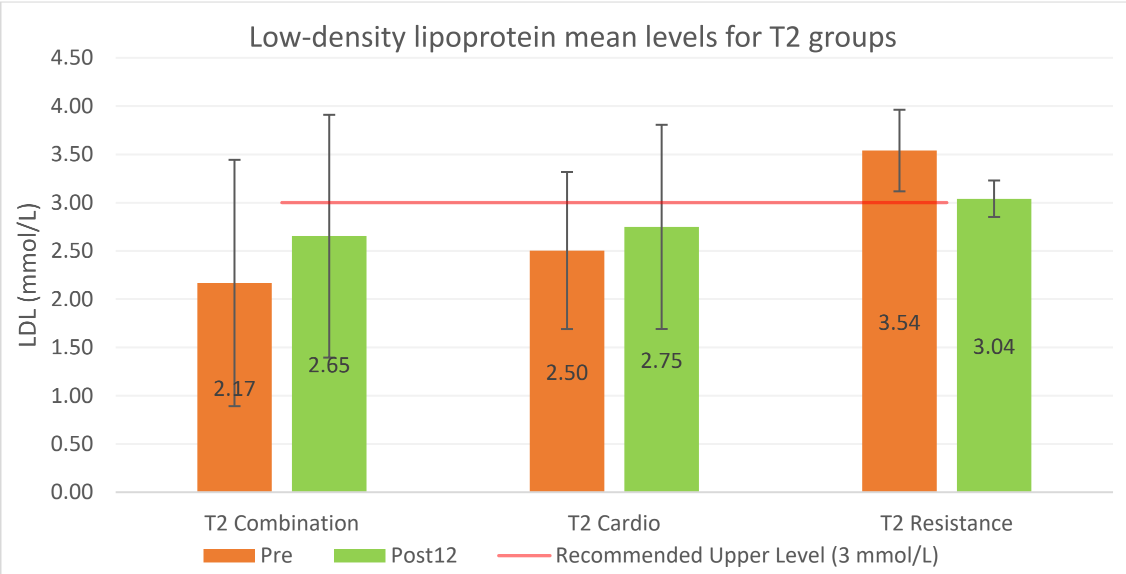

Figure 41, displays a column graph showing the pre and post exercise programme results for LDL (mmol/L) mean and standard deviation of each T2 volunteer control group. NHS recommended healthy level shown (NHS, 2019a).

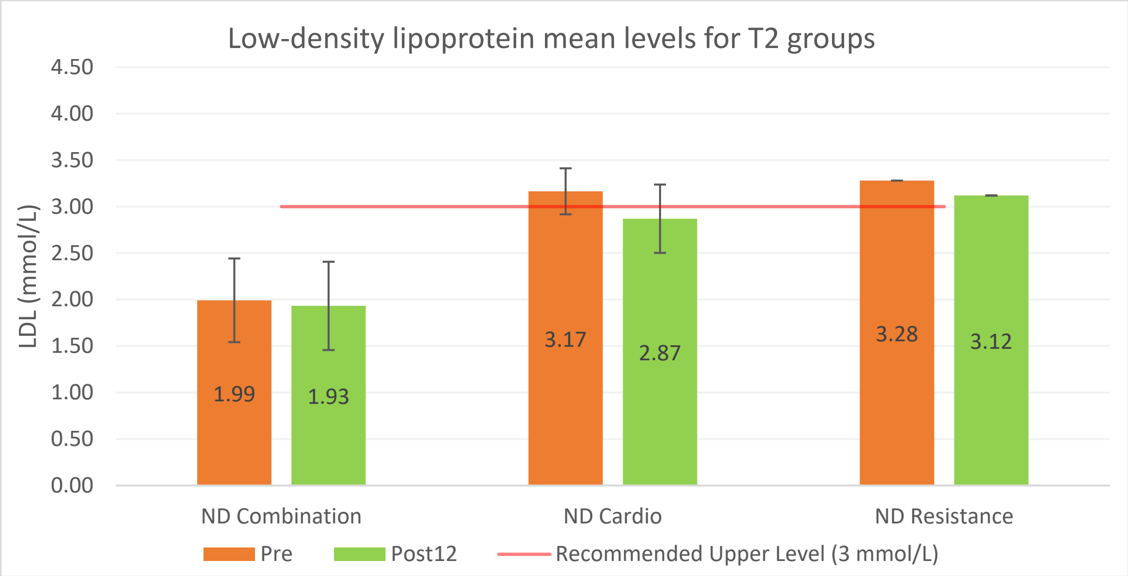

Figure 42, displays a column graph showing the pre and post exercise programme results for LDL (mmol/L) mean and standard deviation of each ND volunteer control group. NHS recommended healthy level shown (NHS, 2019a).

The comparison of Figure 41 and Figure 42 for the T2 and ND groups LDL mean result after intervention are as follows.

- Figure 41 shows T2 combination and cardio both increased however they were both below the recommended upper level at baseline. Whereas T2 resistance group which was above the recommended level showed a large decrease from 3.54 to 3.04 mmol/L.
- All ND groups decreased in Figure 42. ND cardio reduced from above the recommended level at 3.17 mmol/L to below it 2.87 mmol/L.

3.3.11 Blood pressure systolic and diastolic

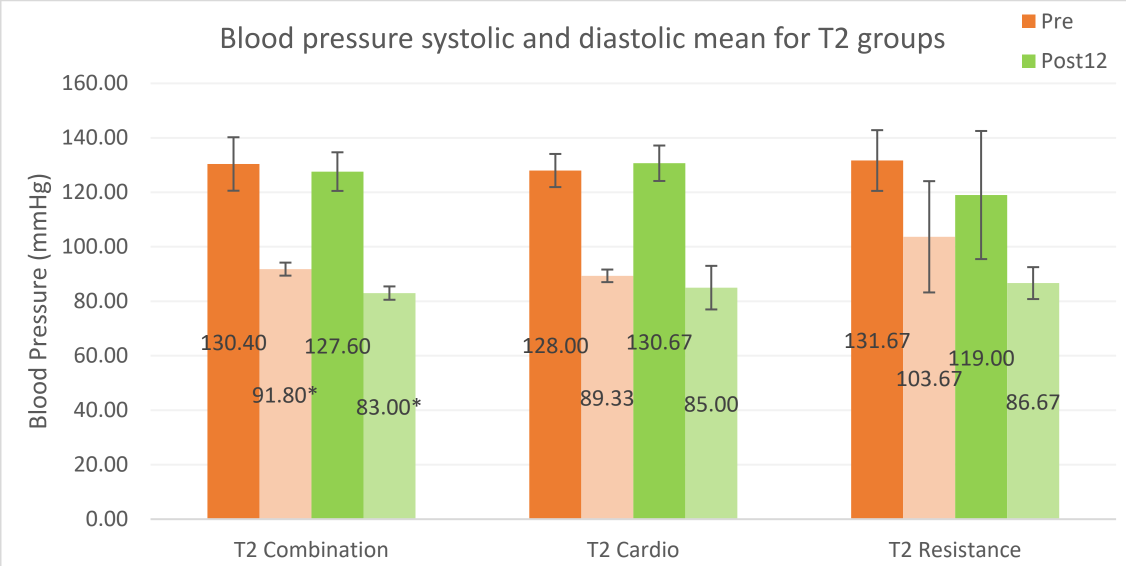

*Figure 43, displays a column graph showing the pre and post exercise programme results for blood pressure systolic and diastolic (mmHg) mean and standard deviation of each T2 volunteer control group. Systolic is displayed as the darker shade whilst diastolic is displayed as the lighter shade. (*p < 0.05)*

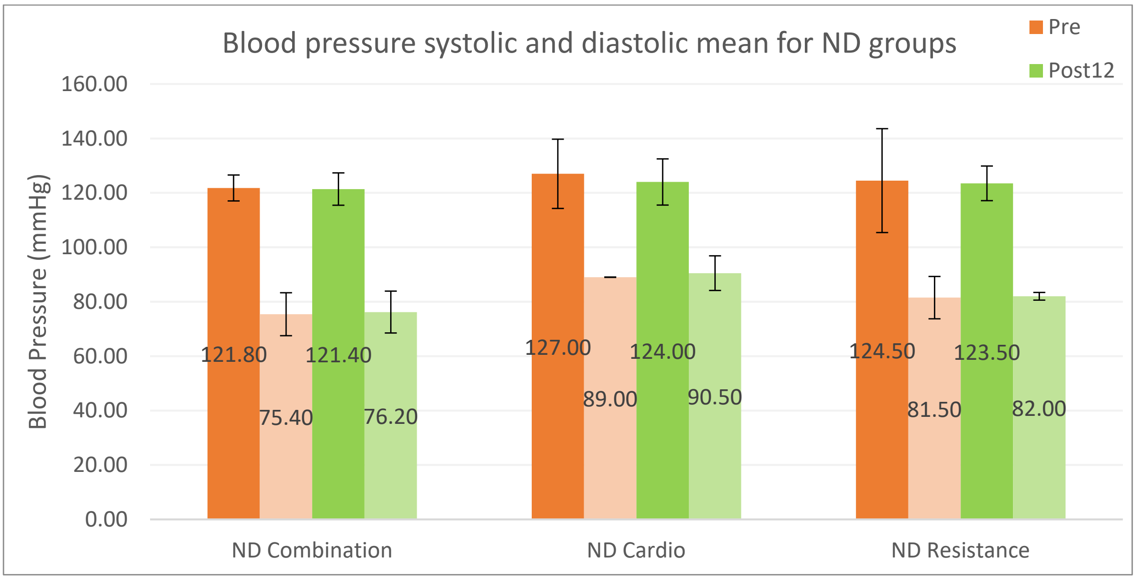

Figure 44, displays a column graph showing the pre and post exercise programme results for blood pressure systolic and diastolic (mmHg) mean and standard deviation of each ND volunteer control group. Systolic is displayed as the darker shade whilst diastolic is displayed as the lighter shade.

The comparison of Figure 43 and Figure 44 for volunteer groups mean blood pressure systolic and diastolic results before and after intervention are as follows.

- The T2 combination group showed statistical significance between pre and post diastolic blood pressure with a p-value of 0.001. Blood pressure diastolic mean reduced from 91.88 to 83 mmHg.
- The T2 resistance group shows the largest reduction in blood pressure from 131.67/103.67 to 119.00/86.67 mmHg.

In Arora's study spoken about earlier, the PRT group experienced a decrease in systolic blood pressure from 126 to 118 mmHg whilst the equivalent T2 resistance group showed a decrease from 131.67 to 119.00 mmHg which corelates with this study.

The AE group in Arora's study showed a decrease in systolic blood pressure mean values from 183 to 172 mmHg whilst in this current study the equivalent T2 cardio group experienced an increase from 128 to 130.67 mmHg. This may be due to the fact that in Arora's study the volunteers exercise more frequently, three times per week instead of two times per week and had a 2 week longer intervention duration (Arora, Shenoy and Sandhu, 2009).

3.4 One-repetition maximum

*Table 7, Shows the mean and standard deviation 1RM pre and post intervention results for each control group. (*p < 0.05).*

	Pre		Post12			
T2 Combination	**mean**	**sd**	**mean**	**sd**	**difference**	**p-value**
Squat	117.76	43.11	146.09	55.45	28.33	0.190
Chest press	63.07	31.01	88.49	20.32	25.42	0.184
Back pull down	67.19	1.14	73.30	11.73	6.11	0.564
Tricep pull down	34.17	11.03	40.19	9.21	6.02	0.134
Bicep curl	29.54	4.49	36.02	1.87	6.48	0.177
T2 Cardio						
Squat	58.07	8.21	58.07	8.21	0.00	
Chest press	42.22	9.36	43.17	9.83	0.94	0.204
Back pull down	42.30	5.58	42.78	6.34	0.49	0.423
Tricep pull down	22.40	3.47	22.83	3.04	0.43	0.423
Bicep curl	22.83	6.08	26.12	5.60	3.29	0.185
T2 Resistance						

Squat	49.72	5.66	80.76	16.42	31.03	0.058
Chest press	65.09	6.17	87.10	3.00	22.01	0.036*
Back pull down	53.74	12.15	62.76	9.94	9.02	0.130
Tricep pull down	30.23	3.39	40.66	6.26	10.44	0.099
Bicep curl	29.41	4.59	33.24	4.60	3.83	0.042*
ND Combination						
Squat	69.17	16.28	111.78	20.86	42.61	0.024*
Chest press	53.11	22.28	68.13	16.36	15.02	0.038*
Back pull down	43.29	8.24	48.56	6.80	5.27	0.030*
Tricep pull down	23.95	5.86	27.92	7.60	3.97	0.077
Bicep curl	22.32	8.02	26.97	8.65	4.65	0.059
ND Cardio						
Squat	37.75	12.32	60.98	28.74	23.23	0.295
Chest press	33.39	2.05	33.39	2.05	0.00	
Back pull down	26.63	14.57	36.88	7.47	10.25	0.290
Tricep pull down	15.32	0.68	18.41	3.70	3.09	0.500
Bicep curl	15.10	0.99	15.55	0.35	0.45	0.500
ND Resistance						
Squat	104.84	49.72	145.18	65.70	40.34	0.174
Chest press	70.18	17.12	87.11	8.21	16.93	0.227
Back pull down	55.46	11.37	68.70	7.76	13.25	0.121
Tricep pull down	30.64	1.37	36.91	0.04	6.26	0.100
Bicep curl	28.97	3.71	33.17	0.72	4.20	0.297

The comparison of T2 and ND group mean 1RM before and after intervention mean results shown in Table 7 are as follows.

- In Table 7 1RM mean results pre and post intervention are shown. The greatest increase in 1RM mean was the ND combination groups squat which increased after intervention from 69.17 to 111.78 kg and shows a statistically significant difference with a p-value of 0.024.
- The greatest increase involving T2 volunteers occurred in the T2 resistance group mean squat 1RM which increased from 49.72 to 80.72 kg after intervention and was very close to showing a statistically significant difference with a p-value of 0.058.

- The mean T2 resistance group chest press 1RM increased after intervention from 65.09 to 87.10 kg and shows a statistically significant difference with a p-value of 0.036.
- The mean T2 resistance groups bicep curl 1RM increased from 29.41 to 33.24kg after intervention and shows a statistically significant difference with a p-value of 0.042.
- The T2 cardio group squat 1RM mean and ND cardio group chest press mean 1RM experienced no increase whilst the other cardio groups mean increases were much smaller than the combination and resistance exercise groups that involved resistance.
- The ND combination groups mean chest press 1RM increased from 53.11 to 68.13 kg after intervention and shows a statistically significant difference with a p-value of 0.038.
- The ND combination groups mean back pull down 1RM increased from 43.29 to 48.56 kg after intervention and shows a statistically significant difference with a p-value of 0.03.
- The ND combination bicep curl mean 1RM after intervention increased from 22.32 to 26.97 kg and was very close to showing statistically significant difference with a p-value of 0.059.

The T2 cardio group experienced much smaller mean 1RM increases than the T2 combination and T2 resistance groups. This supports the theory that resistance exercise increases muscle mass and strength. These results correlate with a previous study performed by Mangine which show that 8 weeks of low volume resistance exercise experience increases in 1RM (Mangine et al., 2015).

3.5 Immuno-assay results performed using the Randox Investigator

In this section the results are presented for metabolic syndrome assays 1 and 2 shown in Table 6. The ND combination group in this section was taken from means from a lab data bank therefore there are no standard deviation or p-values for this group. The Randox Investigator is a very useful machine as you can do many tests at once and has built in standards and controls. Diabetic people are a varied population and there was not a large enough sample size to break down into groups therefore the standard deviations are large.

3.5.1 Interleukin 6

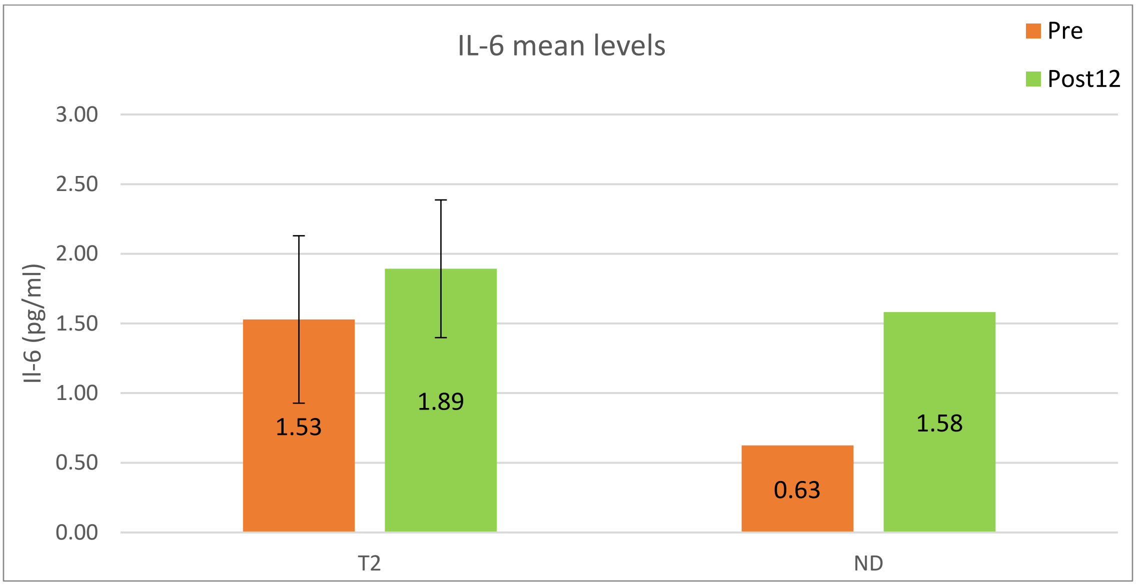

Figure 45, displays a graph showing before and after intervention mean results for IL-6 levels of T2 and ND combination groups.

The comparison of the T2 and ND combination groups before and after intervention of mean IL-6 results shown in Figure 45 are as follows.

- IL-6 levels for both T2 volunteers increased after intervention.
- T2 volunteers IL-6 mean levels after intervention increased from 1.53 to 1.89 pg/ml.

- ND volunteers IL-6 mean levels after intervention increased from 0.63 to 1.58 pg/ml.

A study by Kadoglou et al. in 2007 showed that IL-6 levels reduced after exercise training in T2DM volunteers from 4.51 to 2.98 pg/ml which opposes the increase in IL-6 mean results after intervention shown in this current study (Kadoglou et al., 2007). However, normal IL-6 levels are 5-15 pg/ml (Alecu et al., 1998).

Balducci et al. found that a combined exercise programme reduced IL-6 which opposes this study (Joint Formulary Committee, September 2018; Balducci et al., 2010). A study by Castaneda et al. showed that Il-6 levels decreased by 4.2 pg/l after 12 weeks of resistance exercise (Castaneda et al., 2004).

3.5.2 Leptin

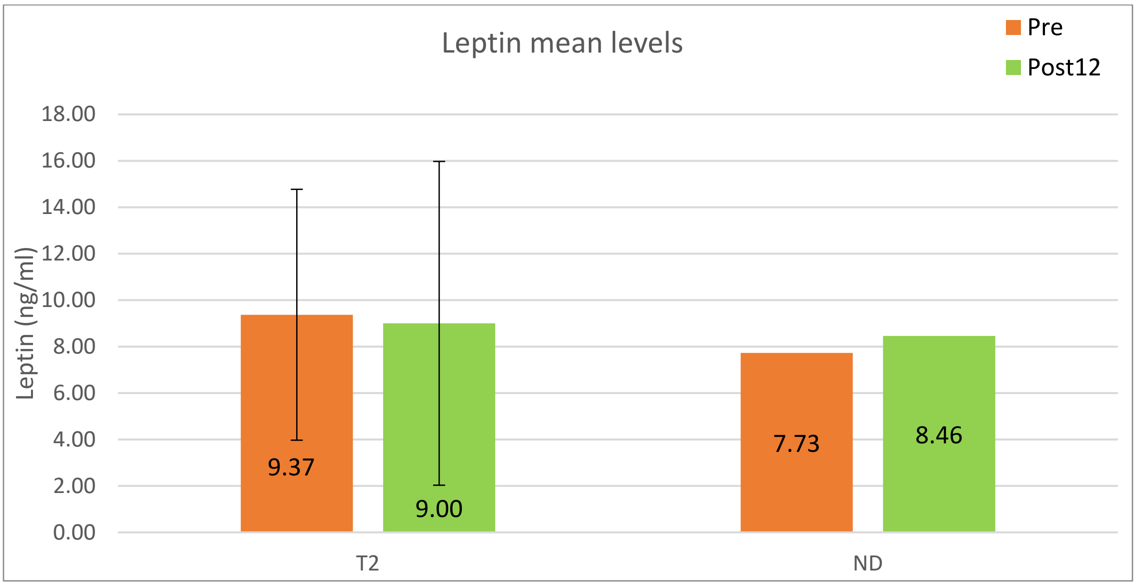

Figure 46, displays a graph showing before and after intervention mean results for leptin levels of T2 and ND combination groups.

The comparison of the T2 and ND combination groups before and after intervention of mean leptin results shown in Figure 46 are as follows.

- Leptin levels decreased in the T2 volunteer group after intervention from 9.37 to 9.00 ng/ml.
- The ND volunteer group mean leptin levels increased after intervention from 7.73 to 8.46 ng/ml.

Balducci et al. found that a combined exercise programme reduced leptin which supports the T2 group results (Joint Formulary Committee, September 2018; Balducci et al., 2010). Leptin was higher in women with gestational diabetes than in women with normal glucose tolerance (Kautzky-Willer et al., 2001). Leptin may play an important role in regulating body weight by signalling the size of the adipose tissue mass. Leptin was found to be highly correlated with BMI. Weight loss due to food restriction was associated with a decrease in leptin (Maffei et al., 1995). In Al sultan, Leptin levels positively correlated with BMI and hip circumference (Al-Sultan and Al-Elq, 2006). A study by Becic et al. showed that aerobic exercise reduced leptin levels by 1.89 ng/mL (Becic, Studenik and Hoffmann, 2018). Normal leptin ranges for healthy males are 1.2 to 9.5 ng/mL whilst normal ranges for females are 4.1 to 25 ng/mL. All results displayed in this study show leptin levels within the normal range.

3.5.3 Resistin

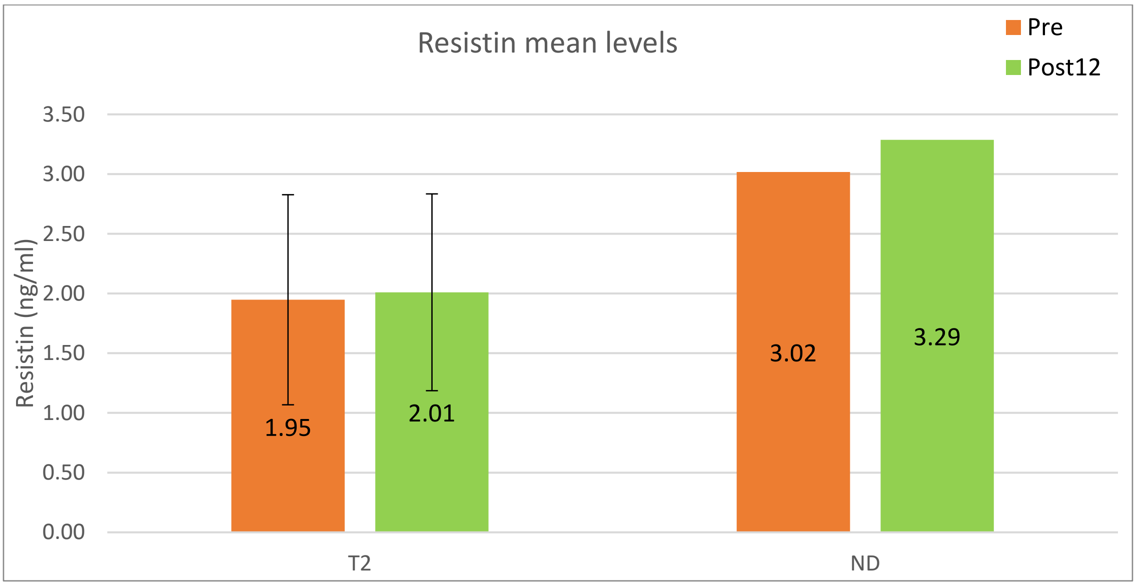

Figure 47, displays a graph showing before and after intervention mean results for resistin levels of T2 and ND combination groups.

The comparison of the T2 and ND combination groups before and after intervention of mean resistin results shown in Figure 47 are as follows.

- Figure 47 shows that both T2 and ND combination groups before and after intervention of a structured exercise programme experienced increases in resistin levels.
- The T2 combination group increased resistin mean levels from 1.95 to 2.01 ng/ml
- The ND combination group increased resistin mean levels from 3.02 to 3.29 ng/ml.

Kadoglou et al. showed that an exercise programme induced considerable reduction of resistin in T2DM individuals. Kadaglous exercise group showed a mean reduction in resistin levels from 17.4 to 11.88 ng/ml. Subgroup analysis revealed that resistin showed a larger difference in male subjects compared with female subjects. Kadoglou's study opposes this current study's results which may have been due to the small sample size of this study (Kadoglou et al., 2007). This current study showed lower levels than the normal published normal resistin ranges from 7.25 to 15.68 ng/ml (Lausten-Thomsen et al., 2017).

Balducci et al. found that a combined exercise programme reduced resistin (Joint Formulary Committee, September 2018; Balducci et al., 2010). This opposes this current study.

3.5.4 TNFα

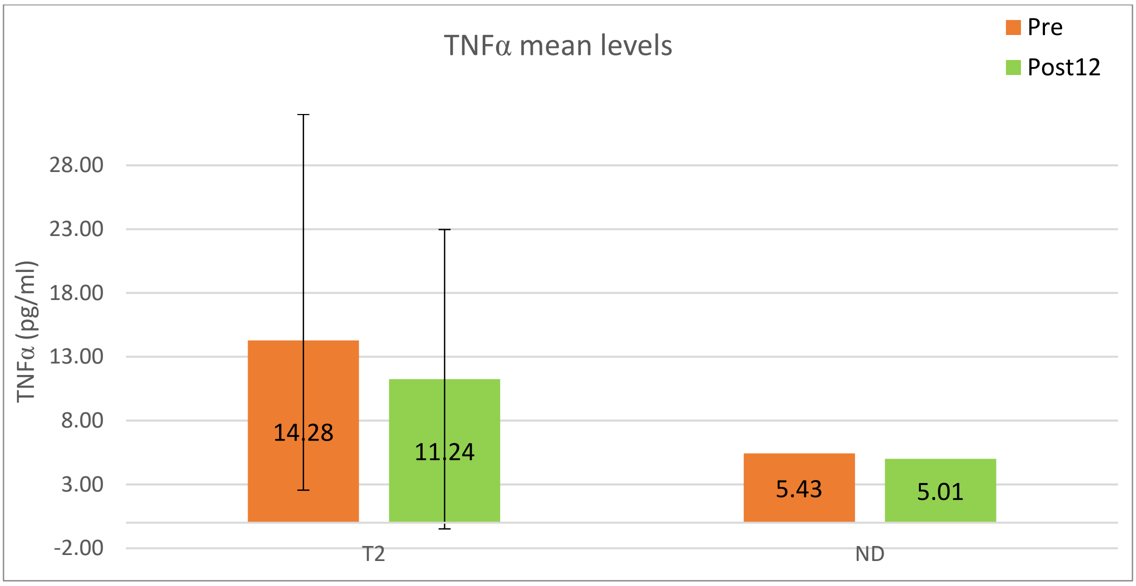

Figure 48, displays a graph showing before and after intervention mean results for TNFα levels of T2 and ND combination groups.

The comparison of the T2 and ND combination groups before and after intervention of mean TNFα results shown in Figure 48 are as follows.

- Figure 48 shows that both T2 and ND groups before and after intervention of a structured exercise programme experienced decreases in TNFα levels.
- The T2 group experienced a decrease after intervention of 14.28 to 11.14 pg/ml.
- The ND group after intervention shows a decrease from 5.43 to 5.01 pg/ml.

Balducci et al. found that a combined exercise programme reduced TNFα which correlates with this study (Joint Formulary Committee, September 2018; Balducci et al., 2010). Normal TNFα levels are 0-16 pg/ml (Alecu et al., 1998).

3.5.5 C-reactive protein

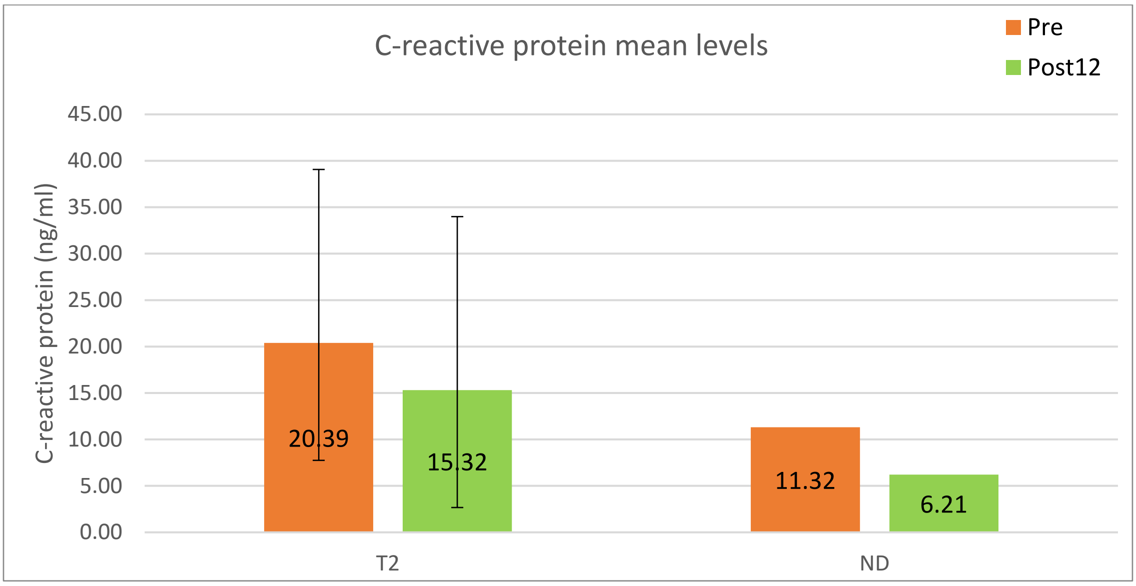

Figure 49, displays a graph showing before and after intervention mean results for C-reactive protein levels of T2 and ND combination groups.

The comparison of the T2 and ND combination groups before and after intervention of mean C-reactive protein results shown in Figure 49 are as follows.

- Figure 49 shows that both after intervention T2 and ND groups experienced decreases in CRP levels.
- The T2 group decreased from 20.39 to 15.32 ng/ml which are much higher than the normal CRP levels for healthy adults.
- The ND group decreased from 11.32 to 6.21 ng/ml which are much higher than the normal CRP levels for healthy adults.

Resistin levels are much higher in T2DM volunteers than in healthy subjects and correlates with IL-6 and CRP levels in T2DM individuals (Abate et al., 2014). Balducci et al. found that physical activity is effective in reducing CRP levels in T2DM patients (Balducci et al., 2010). Balduci's study correlates with this current study. A study by Castaneda et al. showed that CRP levels decreased by 1.7 mg/l after 12 weeks of resistance exercise (Castaneda et al., 2004). These results correlate with this current study. Normal CRP levels for healthy young adult volunteers are 0.8 mg/L, which is similar to this study's ND group mean CRP results (Shrivastava et al., 2015).

3.5.6 Cystatin C

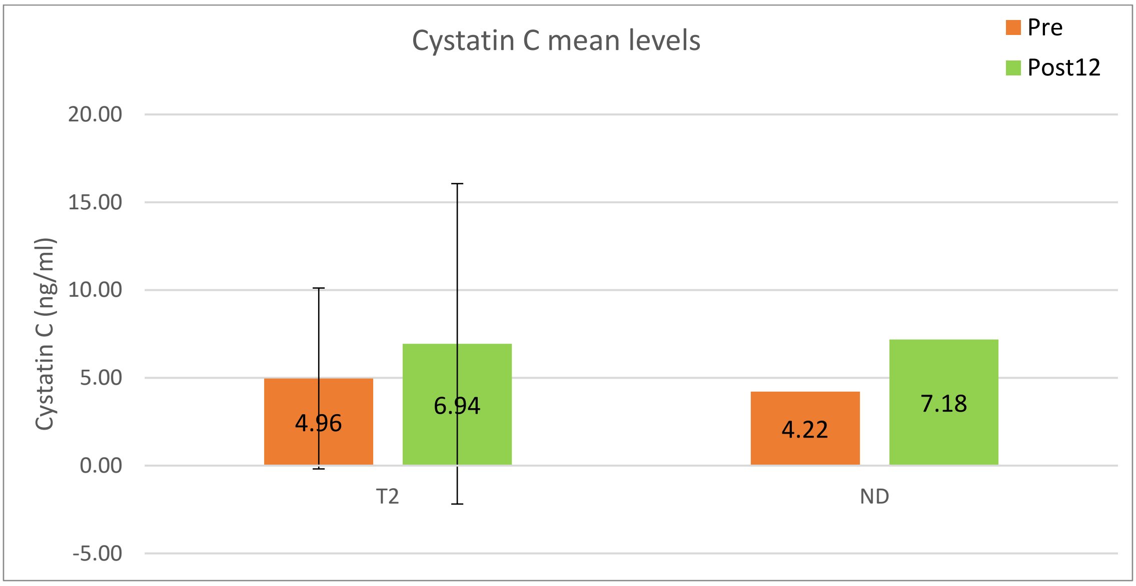

Figure 50, displays a graph showing before and after intervention mean results for Cystatin C levels of T2 and ND combination groups.

The comparison of the T2 and ND combination groups before and after intervention of mean Cystatin C results shown in Figure 50 are as follows.

- Figure 50 shows cystatin c level increases after intervention in both T2 and ND groups.
- The T2 group after intervention shows an increase of cystatin c levels from 4.96 to 6.94 ng/ml.
- The ND group cystatin C levels increased after intervention from 4.22 to 7.18 ng/ml.

A study by Peachter et al. involving 12 weeks of low intensity aerobic exercise in a swimming pool twice a week showed decreases in cystatin C levels from 1.7 to 1.4 mg/l after intervention (Pechter et al., 2003). Normal cystatin C ranges are from 0.6-1 mg/l (Villa et al., 2005).

In the immuno-assay results produced the large standard deviation was due to small sample size. For a future study a larger sample size would show a better representation of the T2DM population. This would be calculated by the performance a power calculation which would generate a total number of volunteers required to compose a statistically rigid study and would generate a picture which can be considered as a representation of the T2DM population. Furthermore, these results could have been divided into different subgroups such as gender, medication information or diagnosis diabetes for a detailed subgroup analysis.

Chapter 4 Conclusion

At the start of the thesis there were 3 research questions which were;

1, Does the intervention of a structured exercise programme affect T2DM volunteers compared to non-diabetic volunteers?

2, How do different types of structured exercise programmes affect T2DM volunteers compared to non-diabetic volunteers?

3, How inflammatory markers are affected by a structured exercise programme involving a combination of cardio and resistance exercise in T2DM volunteers compared to non-diabetic volunteers?

The first 2 research questions are answered in the following manner. To conclude this investigation this study shows that after performing the 6-week structured exercise programme T2 combination groups OGTT area under the curve BG concentrations decreased from 1612.40 to 1354.10 mmol/L*min. The T2 cardio group showed a decrease in OGTT area under the curve BG concentration by 1285.17 to 1151.83 mmol/L*min. The T2 resistance group showed a reduction in OGTT area under the curve BG concentration from 1288.55 to 1129.67 mmol/L*min. After completing a structured exercise programme involving combination exercise the T2 group cardio group demonstrated a greater reduction in the area under curve of 258.3 mmol/L*min compared to the other two T2 exercise groups performing cardio and resistance training which reduced 133.34 mmol/L*min and 158.88 mmol/L*min respectively. The ND combination and ND resistance group showed a reduction of 54.5 mmol/L*min and 59 mmol/L*min respectively whilst the ND cardio group showed an increase of 12.5 mmol/L*min. All the T2 cohorts demonstrated a greater reduction in areas under the curve compared to the ND cohorts, across the various exercise subgroups. The overall OGTT total area under the curve are much greater in T2 cohorts than the ND cohorts. The overall OGTT total area under the curve at baseline are much greater than after intervention in all groups except ND cardio.

This study shows that after performing a 6-week structured exercise programme the OGTT time to peak in the T2 resistance group showed a noticeable improvement in response time from 80 to 47 minutes. The T2 combination group showed an improvement in OGTT time to peak from 76 to 58 minutes whilst the OGTT time to peak for T2 cardio group increased slightly from 60 to 67 minutes. The ND combination group showed no change in time to peak. The ND cardio group showed a slight increase in time to peak from 40 to 50 minutes. The ND resistance group showed a slight increase from 35 to 50 minutes. Interestingly, the ND cohort showed a slower time to peak in glucose concentration after participating in the 6-week structured exercise programme.

This study shows that after performing a 6-week structured exercise programme OGTT peak levels in the T2 resistance group decreased by 2.5 mmol/L. The T2 combination group decreased by 1.8 mmol/L whilst the T2 cardio group decreased 1.56 mmol/L. The ND cardio groups increased by 0.85 mmol/L after intervention. The ND combination and resistance group reduced by 0.10 mmol/L and 0.15 mmol/L respectively. All the T2 cohorts displayed a reduction in their OGTT peak glucose concentrations.

After a structured exercise programme of 6-weeks the group that showed the greatest reduction in mean HbA1c levels was the T2 combination group which reduced by 4.6 mmol/mol compared to the ND combination group which reduced HbA1c mean by 1.2 mmol/mol. The T2 cardio group reduced HbA1c mean by 2 mmol/mol compared to the ND cardio group which reduced by -0.5 mmol/mol. Interestingly the T2 resistance group showed an increase in mean HbA1c levels by 0.67 mmol/mol whilst the ND resistance group showed no change which suggests that resistance training alone does not benefit HbA1c levels across the 6-week period. The overall HbA1c levels are greater in T2 cohorts than the ND cohorts.

Weight decreased 2.58 kg in the T2 combination group after intervention and showed a statistically significant reduction with a p-value of 0.049 whilst the ND combination group showed a slightly smaller decrease of 0.86 kg. Both T2 and ND cardio and groups decreased by 1.61 kg and 1.5 kg respectively. Both T2 and ND resistance groups showed increases in weight of 0.43 kg and 1.3 kg respectively.

Total cholesterol mean levels decreased in the T2 resistance group after intervention of a structured exercise programme and showed a statistically significant reduction from above the recommended level to below the recommended level from 5.34 to 4.68 mmol/L with a decrease of 0.66 mmol/L. Whilst the T2 combination and cardio group showed slight increases in total cholesterol of 0.14 mmol/L and 0.37 mmol/L respectively. All the ND groups remained fairly constant. The T2 cardio group showed an increase in HDL mean levels after intervention from 1.30 to 1.43 mmol/L Whilst the T2 combination and resistance group showed slight decreases. Whereas the ND combination and resistance groups both showed slight increases in HDL mean levels after intervention. Both T2 combination and resistance groups showed light decreases in triglyceride levels of 0.12 mmol/L and 0.07 mmol/L respectively, as did both ND combination and resistance groups with decreases of 0.09 mmol/L and 0.12 mmol/L respectively. The ND cardio group showed an increase of 0.27 mmol/L. The LDL levels in the T2 resistance group showed a decrease from above the recommended level to below the recommended level in mean LDL of 0.50 mmol/L whilst both T2 combination and cardio groups showed increases of 0.48 mmol/L and 0.25 mmol/L respectively. All ND groups showed decreases in LDL whilst ND cardio and resistance groups showed decreases from above the recommended level to below the recommended level.

The ND combination group displayed a statistically significant reduction in FBG levels after performing a single bout of exercise from 5.4 to 4.9mmol/L with a p-value of 0.024. The ND combination group showed a statistically significant difference in PPBG of 1 exercise session from 6.30 to 5.28 mmol/L with a p-value of 0.042406. The ND combination group showed a statistically significant reduction in PPBG after 12 exercise sessions from 6.3 to 4.9 mmol/L with a p-value of 0.016. The ND resistance group also showed a statistically significant reduction between pre and post12 PPBG mean results from 5.8 to 5.15 mmol/L with a p-value of 0.049.

The third research question was answered in the following manner. Interleukin mean levels increased after intervention for both T2 and ND combination groups by 0.26 pg/ml and 0.95 pg/ml respectively. The T2 group showed larger IL-6 values than the ND group however, the ND group displayed a larger increase in IL-6 levels. Leptin mean levels after intervention reduced in the T2 combination group by 0.37 ng/ml whilst the ND group showed an increase of 0.73 ng/ml. The T2 and ND combination groups for resistin both showed slight increases of 0.06 ng/ml and 0.27 ng/ml respectively whilst the ND showed higher levels of resistin than the T2 group. Both T2 and ND groups mean results after intervention for TNFα showed decreases of 3.04 pg/ml and 0.42 pg/ml respectively whilst the T2 groups levels were noticeably higher. CRP mean levels decreased in both T2 and ND groups after intervention by 5.07 ng/ml and 5.11 ng/ml respectively. The T2 group results display much higher levels then the healthy counterparts. Both T2 and ND groups showed increased cystatin C mean levels after intervention of 1.98 ng/ml and 2.96 ng/ml respectively. The cystatin C results showed similar levels for both T2 and ND volunteer groups.

There were no statistically significant differences in metabolic biomarkers for both cohorts across the intervention this may have been due to the small sample size. Testing of a larger sample size would be required to show the biological changes influenced by conducting a regimented exercise programme.

There are various factors that could improve this study such as more frequent exercise sessions, a longer duration, a larger sample size, to record medication and to record diet. The literature that is available shows that a longer duration and an increased frequency of exercise would be beneficial. A diet diary throughout the study would have been valuable data but may have not been accurate as there is no certainty of the honesty of answers from volunteers. Splitting volunteers into groups of specific diet such as high carb and low carb could have been an interesting study but the increased healthy and safety risk that comes with the changing of the volunteer’s diets may have been difficult in terms of ethical approval. Another aspect of the study that could have been improved was the record of medication. The grouping of volunteers could have been dependent on medication which would have been a valuable variable in the study.

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Appendix

Appendix 1 T2DM volunteer information sheet

Leicester School of Pharmacy

Faculty of Health & Life Sciences

Participant Information Sheet Date:01/07/2017

Title of Project: The Use of a Cardio and Resistance Exercise Programme to Assess Immunological and Physiological Parameters in Type 2 Diabetes Mellitus Volunteers.

Principal Investigators: Prof M J Taylor, Dr T Sahota, Dr P Tomlins, Dr R Furmonaviciene, Mr K Chauhan, Mr B Alharbi, Mrs N Alsubaie and Mr A Hill.

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish.

Ask us if there is anything that is not clear or if you would like more information. Please take time to decide whether or not you wish to take part. If you do wish to take part please complete the slip at the end of this sheet.

What is the purpose of the study?

As part of the growing research into Diabetes Mellitus the School of Pharmacy at De Montfort University are working to investigate the effects of a combined exercise programme (cardio and resistance) on blood glucose, metabolic and immunological parameters that could help you with the management of diabetes and increase your insulin sensitivity.

This research involves a combination of two types of exercises and this is where we need your help. We would like to invite you to take part in this study which will help us to understand the role of exercise and how it can help people with diabetes to maintain a healthy body weight, to possibly manage your blood glucose level more effectively and increase insulin sensitivity.

We will keep your information strictly confidential and nobody other than the research team will have access to your personal information.

Before any research goes ahead it has to be checked by De Montfort University Research Ethics Committee. They make sure that the research is fair.

Why have I been invited?

You have been invited to take part in this study because you are at risk or have Type 2 Diabetes and are aged between 18 and 60.

Do I have to take part?

It is up to you to decide. We will answer any questions you have about the study and go through this information sheet. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive from your doctor or hospital.

What will happen to me if I take part?

Preliminary procedures

Before enrolling in the study you will be asked to attend a screening visit where we will:

- Discuss and complete confidential questionnaires regarding your health, family history and physical activity level.
- Measure your blood pressure and heart rate.
- Measure your height and weight
- Provide an opportunity for you to ask questions.
- Familiarise you with equipment to be used in the study and teach you how to use the recumbent ergometer bike and how to lift the weights safely on the multi-gym machine.
- This session will also be used to determine the intensity of exercise during cycling on the recumbent ergometer bike using Heart Rate Reserve (HRR). Also, in this orientation session we will use predicted one repetition maximum (1RM) to determine how much weight for different muscles you should lift in the resistance exercise session later.

These preliminary procedures will enable us to determine whether you are suitable to safely participate in the study or not.

Main experimental trials

The main experimental trial will involve 2 x 1 hour exercise sessions a week for a 6 week period, (exercise session includes rest and final observation of volunteer). Blood glucose levels will be monitored before, during and after each session, using a standard finger prick test. In addition, Cholesterol, High density lipoprotein, low density lipoprotein and Triglyceride will be monitored before, and after each exercise programme using a finger prick test.

Each exercise session will consist of a combined exercise protocol of 30 min of resistance exercise (3 sets of 8 -10 repetitions at 50 – 60% of predicted one-repetition maximum strength 1-RM) using upper and lower muscle groups followed by 20 min moderate cycling at 50 – 60% of pre-determined heart rate reserve (HRR). Heart rate (HR) and rate of perceived exertion (RPE) will be taken in a different time points throughout the exercise trial. We will also perform an Oral Glucose Tolerance test to assess insulin sensitivity at the beginning and end of the programme and blood samples will be screened for other immunological parameters. If you are taking any statin medication then you may also be asked to provide urine samples for analysis in a parallel study~~.~~ We may also ask you to provide a saliva sample for a further study which assesses microbes present in saliva.

Incentives

We would like to offer an incentive of a subsidised gym membership at the De Montfort University's QEII Leisure Centre on completion of 100% of the dates agreed. This is a thank you for your participation but also to help you maintain the healthy exercise regimen until the following year's assessment.

What are the possible benefits of taking part?

As a result of being involved in this study you will receive health and fitness information about yourself including fitness tests and body measurement. You may also witness a decrease in your Hba1c levels and an increase in your insulin sensitivity as well as other general improvements to your health.

The findings of this study will be published in scientific journals so that understanding about how exercise can help people with diabetes to improve their health and control their weight and blood glucose levels. This information may contribute towards improved exercise guidelines for the diabetic patients.

We will provide you with feedback about the main study findings and also about your own results and would be delighted to explain our findings and discuss possible implications with you.

What if there is a problem?

The chance of something going wrong is small. All of the procedures involved in this study are low risk and our screening tests are designed to ensure that you will only participate if it is safe for you to do so. However, if you have any concerns at any time about any aspect of the way you have been approached or treated during the course of this study, you should ask to speak to the researchers who will do their best to answer your questions (contact details below), and the normal De Montfort University complaints mechanisms will be available to you.

Will my taking part in the study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you, which leaves the University, will have your name and address removed so that you cannot be recognised from it.

What will happen if I don't want to carry on with the study?

While we do not expect the programme to cause you to become upset if this does happen then you will have the option to pause or stop your participation immediately, you may continue only if you wanted to. If you withdraw from the study, we will destroy all your identifiable data, but may use the data collected up to your withdrawal.

Who has reviewed the study?

This study has been reviewed and approved by the Faculty of Health and Life Sciences Ethics Committee at De Montfort University. Approval does not guarantee that you will not come to any harm if you take part. However, approval means that the Committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision.

You will be given a copy of this information sheet and a signed consent form to keep for your records.

Contact for Further Information

Any questions about the procedures used in this study are encouraged. If you have any doubts or questions, please ask for further explanations by contacting

Prof M Joan Taylor on 01162 506 317 or mjt@dmu.ac.uk,

Dr Tarsem Sahota on 01162 506 220 or ssahota@dmu.ac.uk

Exercise Physiology Laboratory HB1.29 Hawthorn Building Tel.No: 01162 506 220

Thank you for taking the time to read this Volunteer Information Sheet

DE MONTFORT UNIVERSITY LEICESTER

Leicester School of Pharmacy

Faculty of Health & Life Sciences

Participant Information Sheet

Date:01/07/2017

Title of Project: The Use of a Cardio and Resistance Exercise Programme to Assess Immunological and Physiological Parameters in Volunteers.

Principal Investigators: Prof M J Taylor, Dr T Sahota, Dr P Tomlins, Dr R Furmonaviciene, Mr K Chauhan, Mr B Alharbi, Mrs N Alsubaie and Mr A Hill.

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish.

Ask us if there is anything that is not clear or if you would like more information. Please take your time to decide whether or not you wish to take part. If you do wish to take part please complete the slip at the end of this sheet.

What is the purpose of the study?

As part of the growing research into Diabetes Mellitus the School of Pharmacy at De Montfort University are working to investigate the effects of a combined exercise programme (cardio and resistance) on blood glucose, metabolic and immunological parameters that could help you with the management of diabetes and increase your insulin sensitivity.

This research involves a combination of two types of exercises and this is where we need your help. We would like to invite you to take part in this study which will help us to understand the role of exercise and how it can help people with diabetes to maintain a healthy body weight, to possibly manage your blood glucose level more effectively and increase insulin sensitivity.

We will keep your information strictly confidential and nobody other than the research team will have access to your personal information.

Before any research goes ahead it has to be checked by De Montfort University Research Ethics Committee. They make sure that the research is fair.

Why have I been invited?

You have been invited to take part in the study as a volunteer who has no history of Diabetes Mellitus and are aged between 18 and 60.

Do I have to take part?

It is up to you to decide. We will answer any questions you have about the study and go through this information sheet. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive from your doctor or hospital.

What will happen to me if I take part?

Preliminary procedures

Before enrolling in the study you will be asked to attend a screening visit where we will:

- Discuss and complete confidential questionnaires regarding your health, family history and physical activity level.
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Incentives

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The findings of this study will be published in scientific journals so that understanding about how exercise can help people with diabetes to improve their health and control their weight and blood glucose levels. This information may contribute towards improved exercise guidelines for the diabetic patients.

We will provide you with feedback about the main study findings and also about your own results and would be delighted to explain our findings and discuss possible implications with you.

What if there is a problem?

The chance of something going wrong is small. All of the procedures involved in this study are low risk and our screening tests are designed to ensure that you will only participate if it is safe for you to do so. However, if you have any concerns at any time about any aspect of the way you have been approached or treated during the course of this study, you should ask to speak to the researchers who will do their best to answer your questions (contact details below), and the normal De Montfort University complaints mechanisms will be available to you.

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What will happen if I don't want to carry on with the study?

While we do not expect the programme to cause you to become upset if this does happen then you will have the option to pause or stop your participation immediately, you may continue only if you wanted to. If you withdraw from the study, we will destroy all your identifiable data, but may use the data collected up to your withdrawal.

Who has reviewed the study?

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You will be given a copy of this information sheet and a signed consent form to keep for your records.

Contact for Further Information

Any questions about the procedures used in this study are encouraged. If you have any doubts or questions, please ask for further explanations by contacting

Prof M Joan Taylor on 01162 506 317 or mjt@dmu.ac.uk,

Dr Tarsem Sahota on 01162 506 220 or ssahota@dmu.ac.uk

Exercise Physiology Laboratory HB1.29 Hawthorn Building Tel.No: 01162 506 220

Thank you for taking the time to read this Volunteer Information Sheet

DE MONTFORT UNIVERSITY
LEICESTER

Appendix 3 T2DM consent form

Leicester School of Pharmacy

Faculty of Health & Life Sciences

CONSENT FORM

Patient Identification Number:…………………………………………………………………………….

<u>Title of Project: The Use of a Cardio and Resistance Exercise Programme to Assess Immunological and Physiological Parameters in Type 2 Diabetes Mellitus Volunteers.</u>

Name of Principal Investigator: Prof M J Taylor, Dr T Sahota, Dr P Tomlins, Mr K Chauhan, Dr R Furmonaviciene, Mr B Alharbi, Mrs N Alsubaie and Mr A Hill.

PLEASE SIGN INITIALS IN BOX

1. I confirm that I have read and understood the Participant Information Sheet dated (01/07/2017) for the above study. I have had the opportunity to consider the information, ask questions and had these answered satisfactorily. I understand that agreeing to take part means that I am willing to undertake some exercise and giving samples in the above study.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected.

3. I understand that any information I provide is confidential, and that no information that could lead to the identification of any individual will be disclosed in any reports on the project, or to any other party. No identifiable personal data will be published. The identifiable data will not be shared with any other organisation.

4. I understand that confidentiality can be guaranteed for information which I might disclose in any session or visit I attend. I understand that this information will be used only for the purpose(s) set out in this statement and my consent is conditional on the University complying with its duties and obligations under the Data Protection Act 1998.

5. I agree to take part in the above study.

________________	_________________	__________________
Name of Participant	Date	Signature
________________	_________________	__________________
Name of Researcher	Date	Signature

Appendix 4 ND consent form

Leicester School of Pharmacy

Faculty of Health & Life Sciences

CONSENT FORM

Patient Identification Number for this trial:……………………………………………….…….

<u>Title of Project: The Use of a Cardio and Resistance Exercise Programme to Assess Immunological and Physiological Parameters in Volunteers.</u>

Name of Principal Investigator: Prof M J Taylor, Dr T Sahota, Dr P Tomlins, Mr K Chauhan, Dr R Furmonaviciene, Mr B Alharbi, Mrs N Alsubaie and Mr A Hill.

PLEASE SIGN INITIALS IN BOX

1. I confirm that I have read and understood the Participant Information Sheet dated (01/07/2017) for the above study. I have had the opportunity to consider the information, ask questions and had these answered satisfactorily. I understand that agreeing to take part means that I am willing to undertake some exercise and giving samples in the above study.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected.

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5. I agree to take part in the above study.

________________	_________________	__________________
Name of Participant	Date	Signature
________________	_________________	__________________
Name of researcher	Date	Signature

Appendix 5, Volunteer recruitment poster

DE MONTFORT UNIVERSITY LEICESTER

CAN A COMBINATION OF WEIGHT TRAINING AND CYCLING POSITIVELY AFFECT DIABETES?

Why not volunteer for our study?

We are looking for volunteers at risk or with any form of Diabetes Mellitus between 18-60 to take part in research at De Montfort University. You will receive health and fitness assessments and fully supervised exercise training.

A subsidised gym membership at the DMU QEII Leisure Centre will be available on completion.

CONTACT US
Ashley.Hill@dmu.ac.uk
(0116) 250 6220